Exploring the iceberg of Chronic Lymphocytic Leukaemia:

Towards a better estimation of the burden and quality of care
for CLL patients in the Netherlands.

Esther van den Broek

Colofon

Printing of this thesis was realised with financial support of:
- Netherlands Comprehensive Cancer Organisation
- ErasmusMC
- Roche
- Gilead
- GlaxoSmithKline

Cover design and lay-out by Marlies van Hoof; www.madebymarlies.nl
Printed by Gildeprint

ISBN/EAN 978-94-6108-837-6

Exploring the iceberg of Chronic Lymphocytic Leukaemia:
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Verkenning van de ijsberg van Chronische Lymfatische Leukemie:
Naar een betere schatting van de belasting en kwaliteit van zorg
voor CLL patiënten in Nederland.

Proefschrift
ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van rector magnificus Prof. Dr. H.A.P. Pols
en volgens besluit van het college voor Promoties

De openbare verdediging zal plaatsvinden op
Dinsdag 16 december 2014 om 13.30 uur

door
Esther Cecilia van den Broek - Gerritsen
Geboren te ´s-Hertogenbosch in 1981

Promotiecommissie

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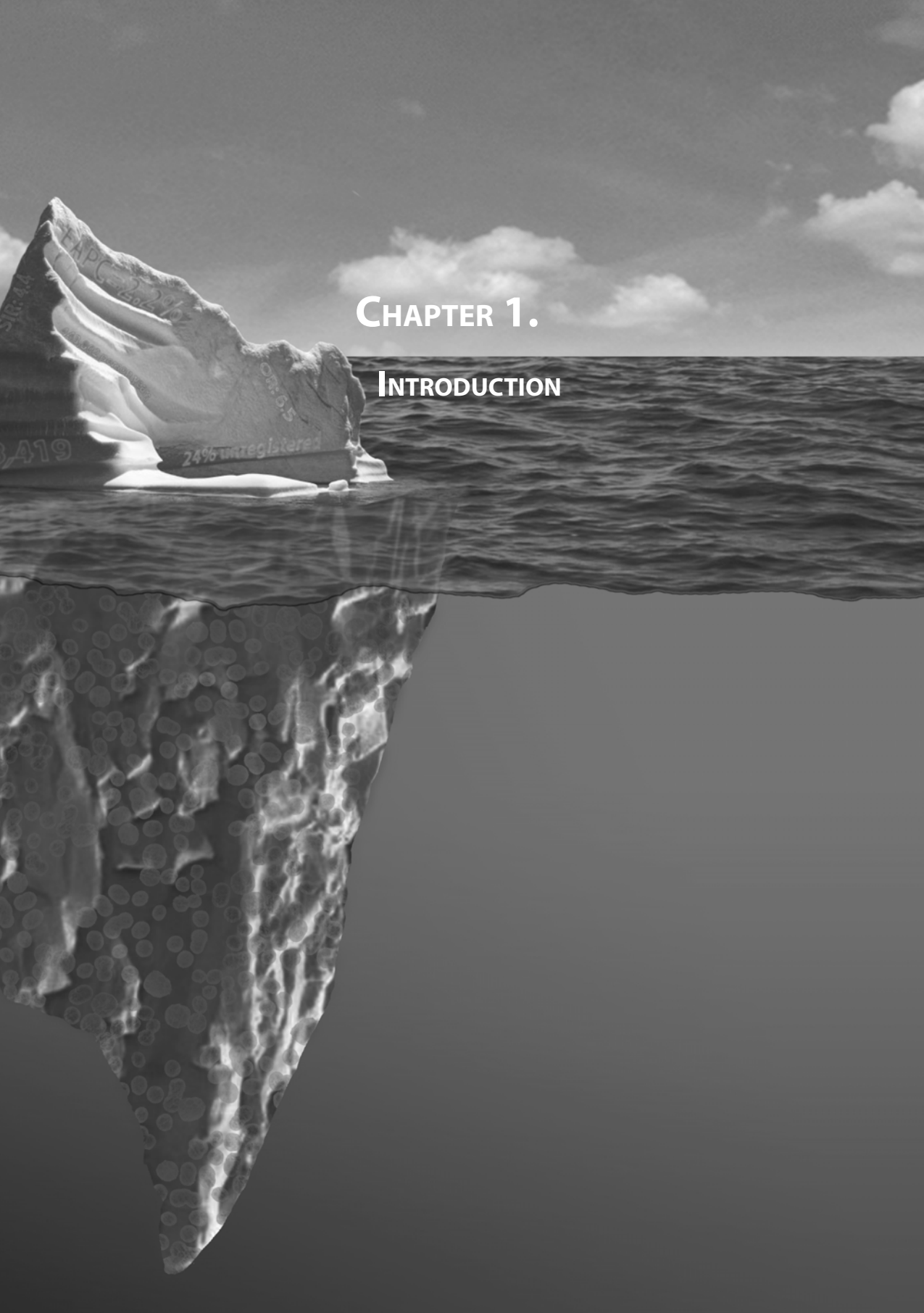

Chapter 1.

Introduction

Introduction

In this thesis, I describe the findings resulting from exploration of the "Chronic Lymphocytic Leukaemia (CLL)-iceberg". In chronic disease epidemiology, the term "Iceberg phenomenon" is used to describe the situation where the number of known, clinical cases of a disease (i.e. the visible tip of the iceberg) is outweighed by those that are still in an unknown, subclinical phase (the larger submerged part of the iceberg).[1]

As most clinical trials only include a small, non-representative proportion of CLL-patients, and underreporting of (mainly indolent) CLL-patients in cancer registries is suspected, the current knowledge about CLL is likely to be affected by the Iceberg-phenomenon.

In order to visualise as much of the submerged part of the CLL-iceberg as possible, I provide information on the burden of CLL. Burden was expressed as incidence, risk of multiple malignancies, mortality and impact on Health-Related Quality of Life (HRQoL). Therefore detection, incidence and survival and the magnitude of the underreporting of CLL in the Netherlands Cancer Registry and its consequences are described. In addition, I present the occurrence of CLL in relation to other malignancies, especially T-cell lymphoma. Lastly, I evaluate the impact of CLL and its treatment on aspects of HRQoL in a population-based setting.

General information

Chronic Lymphocytic Leukaemia (CLL) is a haematological malignancy which can remain undetected for many years and is often detected as a by-product of detection of another serious condition. The survival duration is often long, up to decades.

CLL is characterised by the slow accumulation of monoclonal, mature B lymphocytes carrying CD5, CD19 and CD23 markers. Lymphocytes are components of the adaptive immune response. Unlike most malignancies, the accumulation of malignant lymphocytes is attributed to decreased apoptosis instead of increased proliferation. However, this hypothesis has been challenged in recent years.[2]

Small Lymphocytic Lymphoma (SLL) is an indolent (i.e. slow-growing and causing few symptoms) form of Non-Hodgkin Lymphoma with morphological and immune-phenotypic features similar to CLL. Hence, since 2001, the World Health Organization (WHO) classification scheme for haematopoietic malignancies considers CLL and SLL to be different manifestations of the same disease and combines these entities into one disease category: CLL/SLL.[3] In this thesis CLL/SLL is usually referred to as CLL.

Incidence

Chronic Lymphocytic Leukaemia (CLL) is the most common type of Leukaemia in adults in industrialized western countries, both in terms of incidence and prevalence, with more than 700 diagnoses per year in the Netherlands. Very few patients are below 50 years, more than half of the patients are older than 65 years at the time of diagnosis and men are affected twice as often as women.[4-6]

In the Netherlands, as well as in the rest of Europe, the age-standardized incidence rate of CLL is 3.8 per 100,000 person-years. In the Netherlands the age-standardized incidence rates were 5.1 and 2.5 per 100,000 person-years, for males and females respectively.[6, 7] In the US the incidence rate is higher; 5.1 per 100,000[4], possibly due to higher diagnostic activity, especially in elderly patients.

Signs and symptoms

CLL can have a long, asymptomatic phase. People suffering from CLL often experience general symptoms: Weakness, feeling tired, weight loss, fever, night sweats, enlarged lymph nodes, pain or a sense of "fullness" in the belly due to an enlarged spleen.[8]

Many of the signs and symptoms of advanced CLL occur because the leukaemia cells replace the bone marrow's normal formation of blood cells (haematopoiesis).[9] As a result, people might develop anaemia; shortage of red blood cells. This can cause tiredness, weakness, and shortness of breath. A shortage of blood platelets (thrombocytopenia) can lead to excess bruising, bleeding, frequent or severe nosebleeds, and bleeding gums.

Although the term leukaemia literally means "white blood", referring to the increased level of white blood cells (leukocytes), in fact only one type of leukocytes, B-lymphocytes, are increased. A shortage of the other types of leukocytes increases the risk of infections.

Especially neutropenia (low levels of neutrophilic granulocytes) puts patients at risk of bacterial infection. The same goes for the lack of function of the malignant B-cells, which leads to a condition call hypogammaglobulinaemia, i.e. decreased levels of antibodies.[10]

Besides the displacement of normal haematopoiesis, CLL may also causes deficiencies of blood cells by the formation of abnormal antibodies that attack normal blood cells. This is known as auto-immunity. If the antibodies attack red blood cells, it is known as autoimmune haemolytic anaemia. Less often, the antibodies attack platelets and the cells that make them, leading to thrombocytopenia. Rarely, the antibodies attack white blood cells, leading to leukopenia.[11]

Table 1: *Overview of the different blood cells and their main function*

Blood cells		Main function
Red blood cells (erythrocytes)		Delivering oxygen (O2) to the body tissues
Platelets (thrombocytes)		Stopping bleedings
White blood cells (leukocytes)	Eosinohilic granulocytes	Combating multicellular parasites infections and certain infections
	Basophilic granulocytes	Initiation of inflammatory reactions, combating parasitic infections
	Neutrophilic granulocytes	Combating bacterial infections
	B lymphocytes	Production of antibodies
	T lymphocytes	Several roles in the immune system
	Natural Killer cells	Combating viral infections

Diagnosis and stage distribution

In the past, all that was needed to diagnose CLL was lymphocytosis - a high number of lymphocytes in the blood and bone marrow that did not have any other cause (like infection). This was originally defined as over 15,000 lymphocytes/mm^3 of blood and at least 40% of the bone marrow being made up of lymphocytes. Since about 30 years, for a diagnosis of CLL, the patient must have at least 5,000/mm^3 of monoclonal lymphocytes. Monoclonal means that the malignant cells are identical, as they are the result of multiple cell divisions of one original cancer cell. This can be proven by flow-cytometry.

Some people have monoclonal lymphocytes in their blood, but not enough for the diagnosis of CLL. If someone has less than 5,000 monoclonal lymphocytes (per mm^3), normal counts of red blood cells and platelets, and no enlarged lymph nodes (or enlarged spleen), they have a condition called monoclonal B-lymphocytosis (MBL). Patients with MBL should not be treated. However, about one patient of every 100 per year will evolve to CLL and might need treatment.[12]

The cancer cells of SLL and CLL have similar morphological features and have the same markers (proteins on the surface of the cells), but the localisation differs. In CLL, the monoclonal cells accumulate in the blood, hence the criterion of at least 5,000 monoclonal lymphocytes (per mm^3 blood). In SLL, the accumulation mainly takes place in the lymph nodes. Therefore, the main criterion for the diagnosis SLL is the presence of lymphadenopathy. Furthermore, it

requires the absence of cytopenia caused by a clonal marrow infiltrate and the number of B-lymphocytes in the peripheral blood should not exceed 5,000 lymphocytes (per mm^3). Whenever possible, the diagnosis should be confirmed by histopathological evaluation of a lymph node biopsy. Still, SLL and CLL can be treated the same.

There are 2 different systems for staging CLL; the Rai system[13] and the Binet system[14].
The Rai staging system divides CLL into 5 stages:
Rai stage 0: Lymphocytosis and no enlargement of the lymph nodes, spleen, or liver, and with near normal red blood cell and platelet counts.
Rai stage I: Lymphocytosis plus enlarged lymph nodes. The spleen and liver are not enlarged and the red blood cell and platelet counts are near normal.
Rai stage II: Lymphocytosis plus an enlarged spleen (and possibly an enlarged liver), with or without enlarged lymph nodes. The red blood cell and platelet counts are near normal.
Rai stage III: Lymphocytosis plus anaemia (too few red blood cells; Haemoglobin <6.8 mmol/L), with or without enlarged lymph nodes, spleen, or liver. Platelet counts are near normal.
Rai stage IV: Lymphocytosis plus thrombocytopenia (too few blood platelets; $<100 \times 10^9$/L), with or without anaemia, enlarged lymph nodes, spleen, or liver.
Clinicians separate the Rai stages into low (stage 0), intermediate (stage I and II), and high-risk (stage III and IV) groups when determining treatment options.

In the Binet staging system, CLL is classified according to the number of affected lymphoid tissue groups (neck lymph nodes, groin lymph nodes, underarm lymph nodes, spleen, and liver) and according to whether or not the patient has anaemia or thrombocytopenia.
Binet stage A: Fewer than 3 areas of lymphoid tissue are enlarged, with no anaemia or thrombocytopenia.
Binet stage B: 3 or more areas of lymphoid tissue are enlarged, with no anaemia or thrombocytopenia.
Binet stage C: Anaemia (Haemoglobin <6.8 mmol/L) and/or thrombocytopenia ($<100 \times 10^9$/L) are present.
Both of these staging systems are helpful for determining risk and strategy, and have been in use for many years.

The staging system most often used to describe the extent of non-Hodgkin lymphoma in adults (including SLL) is called the Ann Arbor staging system. Stage I represents involvement of a single lymph node region or lymphoid structure. When two or more lymph node regions on the same side of the diaphragm are involved, the disease is classified as stage II. Stage III patients have involvement of lymph node regions or structures on both sides of the diaphragm. When extra nodal sites are involved stage IV is recorded.

Prognostic factors
The course of CLL is very heterogeneous. Roughly one-third of patients never requires treatment and has a long survival of up to decades. They eventually die from other causes. In another third, an initial indolent phase is followed by disease progression. The remaining third patients exhibit an aggressive disease at the onset and need immediate treatment.[15]

The Rai and Binet staging systems allow discrimination of patients with aggressive disease at onset, but fail to accurately predict which patients among the good prognosis groups will develop progressive disease. Categorizing a patient based on a set of prognostic factors provides complementary information on predictors of disease outcome and survival. A patient may present with one or multiple prognostic markers. Indicators that suggest a poor prognosis may include: High beta2-microglobulin (B2M) expression,[16] presence of an unmutated immunoglobulin variable region (IgVH)[17, 18] (or its' surrogates; high ZAP-70 expression[19] and high CD38 expression20), and certain chromosomal abnormalities. Del(17p) (loss of function of p53), 14q32 translocations and a complex karyotype are correlated with a poor prognosis, del(11q), trisomy 12 and del(6q) predict an intermediate prognosis and normal karyotype or isolated del(13q) are usually predictors of slow progression.[20]

Treatment options

As randomized clinical trials (RCTs) failed to show a statistically significant difference in survival between early versus deferred therapy for patients with asymptomatic, low risk (Rai 0/ Binet A) CLL/SLL active surveillance remains standard practice for these patients,[21] which means every 3 – 12 months, blood cell counts and clinical examinations should be performed.[22]

Whether or not a patient with intermediate (stages I and II) or high risk (stages III and IV) disease according to the modified Rai classification or with Binet stage B or C requires treatment depends on whether there is evidence for progressive or symptomatic disease also called active disease. At least one of the following IWCLL-criteria[23] should be met:

- Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia
- Massive (i.e., at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly
- Massive nodes (i.e., at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
- Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of less than $30x10^9$/L (30,000/µL), LDT should not be used as a single parameter to define a treatment indication. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (e.g., infections) should be excluded.
- Autoimmune anaemia and/or thrombocytopenia, poorly responsive to corticosteroids or other standard therapy.
- Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:
  - Unintentional weight loss of 10% or more within the previous 6 months;
  - significant fatigue (i.e. ECOG PS 2 or worse; inability to work or perform usual activities);

- fevers higher than 38.0°C for 2 or more weeks without other evidence of infection; or
- Night sweats for more than 1 month without evidence of infection.

Hypogammaglobulinaemia or monoclonal or oligoclonal paraproteinaemia does not by itself constitute a basis for initiating therapy. However, it is recommended to assess the change of these protein abnormalities if patients are treated.

Patients with CLL may present with a markedly elevated leukocyte count; however, the symptoms associated with leukocyte aggregates that develop in patients with acute leukaemia (leukostasis syndrome) rarely occur in patients with CLL. Therefore, the absolute lymphocyte count should not be used as the sole indicator for treatment.

Before 1980, the treatment of CLL revolved around chlorambucil, an alkylating agent. The first breakthrough came in the 1980s with the introduction of purine analogues such as fludarabine, followed by the introduction of monoclonal antibodies at the beginning of this century.[24]

For young and fit patients with advanced disease, the combination of fludarabine, cyclophosphamide, and rituximab (FCR) became the standard first line treatment, after a phase III study showed improvement of survival after addition of rituximab (a monoclonal antibody) in 2010.[25] In the Netherlands, chlorambucil is still the first choice for elderly and/or frail patients, as up until recently no RCTs with this group of patients showed improved therapeutic results over chlorambucil.[26] However, in 2014, a RCT among 781 CLL patients with a Cumulative Illness Rating Scale (CIRS) score higher than 6, showed the combination of chlorambucil and obinutuzumab improved overall survival in CLL patients with comorbidities.[27] In table 2 an overview of the most important therapies is given.[28]

Table 2: *Most important therapies in the treatment of CLL*

Class	Name (EU reference year[a])	Current status
Alkylating agents	Chlorambucil (1956)	First choice therapy in elderly, frail patients, with or without an anti-CD20 monoclonal antibody
	Cyclophosphamide (1958)	Component of FCR, first choice therapy in young, fit patients
	Bendamustine (2010)	Regarded as an effective therapy with a favourable toxicity profile, both in monotherapy and in combination regimens
Purine analogues	Fludarabine (1994)	Component of FCR, first choice therapy in young, fit patients
Mitotic inhibitors	Vincristine (1995)	Component of CHOP(-R) / CVP(-R)
Antracycline	Doxorubicin (1996)	Component of FCR, first choice therapy in young, fit patients
Antibodies	Obinutuzumab (The CHMP[b] recommended the granting of the marketing authorisation in 2014)	Obinutuzumab plus chlorambucil is a treatment standard for untreated elderly patients
	Alemtuzumab (2001)	Addition of Alemtuzumab to chemotherapy improves progression-free survival in high-risk patients (i.e. unmutated immunoglobulin heavy chain genes, deletion 17p or 11q, or trisomy 12). However, product is no longer licensed.
	Rituximab (1998)	Component of FCR, first choice therapy in young, fit patients
	Ofatumumab (2010)	has shown some efficacy in patients who became Fludarabine and Alemtuzumab refractory or who have bulky disease
Tyrosine kinase inhibitors	Fostamatinib	Promising drug in phase I/II
	Idelalisib	Promising drug in phase III
	Ibrutinib	showed significant activity in relapsed or refractory patients

a) The EU reference year corresponds to the year of the first marketing authorisation of a medicine containing that active substance or that combination of active substances in the EU, or alternatively the earliest of the known year of the marketing authorisations for a medicine containing that active substance or that combination of active substances.
b) CHMP = Committee for Medicinal Products for Human Use

Survival
Median survival time of CLL patients is 10 years, but it varies widely according to the stage of the disease at detection or diagnosis and can range from about 1 year to more than 20 to 30 years. The median survival time is more than 10 years for patients with low risk CLL, 7 years for patients with intermediate risk and 18 months to 3 years for patients with high risk CLL.[22] Survival is expected to improve with new treatment options.

Netherlands Cancer Registry
Information on treatment, quality of life and prognosis of CLL patients is mostly gathered in clinical trials. This is a good method for evaluating the efficacy of treatment in selected patient groups, but might not be valid for every day practice, where patients are older and often suffer from comorbidities. Population-based data is very suitable to gain insight into the treatment and its effects in a non-selected, every day practice situation.

Since 1989 the whole Dutch population is covered by the Netherlands Cancer Registry (NCR), started since 1984. The NCR gets notifications of

- All newly diagnosed malignancies by the nationwide network and registry of histo-and cytopathology in the Netherlands (PALGA),
- Haematology departments and laboratories,
- Radiotherapy institutes,
- The national registry of hospital discharge diagnoses (LMR).

Trained registration clerks actively collect data on diagnosis, stage and primary treatment (started within 6 months from diagnosis) from hospital records. For most tumours completeness is estimated to be at least 95%[29] and lower in elderly with deeply located tumours with a clinical, e.g. radiological diagnosis only who were never admitted in a hospital. Information on the vital status of the patients is obtained from hospitals and deaths appearing in official nationwide municipal records. The records provide virtually complete coverage of all deceased citizens of the Netherlands.

However, regarding the registration of CLL patients there are a few pitfalls. Unlike the majority of other malignancies, the definite diagnosis of CLL does not require pathological confirmation, eliminating PALGA as the most important signalling source. In addition, the majority of CLL patients do not require treatment for their disease at the time of diagnosis and the disease can be managed without hospitalisations.

PHAROS
The main objective of the Population-based HAematological Registry for Observational Studies (PHAROS; www.pharosregistry.nl) is to evaluate treatment variation and impact of new drugs and their cost effectiveness in a population based setting. To achieve this, a dataset (supplemental to the NCR) that can be used for this purpose was established. PHAROS enables insight in diagnostic strategies, treatment choices and outcomes in the first, second, third and following lines, adherence to guidelines and effectiveness of therapies in frail and/or elderly patients. For the PHAROS Registry the NCR was used to select all patients in three areas covering approximately 40% of the Dutch population, of at the time interested

regional CCC's with haematological malignancies like CLL, Multiple Myeloma, Diffuse Large B-Cell Lymphoma and Follicular Lymphoma, since 2009; since 2011 they were followed at a national basis by CML, Myelodysplasia and Myeloproliferative conditions. NCR-data of these patients were enriched with details on stage, and longitudinal data such as (response to) treatment and adverse events and conditions. Due to the long intervals prior and between actual treatment, documentation of therapy in CLL patients requires a long follow-up time with multiple registration moments.

Besides PHAROS, a comprehensive cost calculation was performed by researchers of the Institute for Medical Technology Assessment in Rotterdam. They found that, although patients were treated with expensive chemo(immuno-)therapy, the main cost driver was inpatient days for other reasons than administration of chemo(immuno-)therapy.

PROFILES

'Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES)' is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors. HRQoL and other patient reported outcome data were also collected from a normative population of 2,040 individuals from the general Dutch population (CentER panel). This cohort is considered representative for the Dutch-speaking population in the Netherlands.[30] Researchers from the Comprehensive Cancer Centre South (IKZ) in Eindhoven and Tilburg University, The Netherlands, have been working together since 2006 with medical specialists from the local hospitals in order to setup this registry.

PROFILES was built to increase the knowledge on the impact of cancer on people's lives across the whole cancer continuum. The primary goals of studies that use the PROFILES registry are:

1. To assess psychosocial risk and outcome in order to enable identification of patients at high risk for poor physical and mental health outcomes,
2. To analyse mediating mechanisms to better understand the biological and behavioural factors associated with cancer treatment outcomes, and
3. To evaluate physical and psychosocial care needs of cancer survivors.

Results of HRQoL studies using patient reported outcomes might contribute to better care and aftercare for both patients and survivors, as has been suggested in the past[31, 32], if data are collected appropriately, among a representative sample of patients with a good compliance.

Outline

As most clinical trials only include a small, non-representative proportion of CLL-patients, and underreporting of (mainly indolent) CLL-patients in cancer registries is suspected, the current knowledge of the burden of CLL is limited to a subset of the most severe, clinical patients. In chronic disease epidemiology, the situation where the number of known, clinical cases of a disease is outweighed by those that are still in an unknown, subclinical phase, is referred to as the Iceberg phenomenon.[1] The unobserved below surface part of an iceberg usually is much larger than the part visible above the water. The submerged part of the iceberg is likely to hold very relevant information e.g. of disease precursors, preclinical

conditions and early clinical stages. It is even not unthinkable that if the disease is identified at an earlier, preclinical stage, a cure is possible in the future. The main objective of this thesis was therefore to explore the "CLL-iceberg" and visualise as much of the submerged part as possible. To achieve this, the following sub-goals were set:

1a. to provide information on the burden of CLL by studying detection, incidence and survival
1b. to investigate the magnitude of the underreporting of CLL in the Netherlands Cancer Registry and its consequences
2. To uncover the occurrence of CLL in relation to other malignancies, especially T-cell lymphoma.
3. To assess the impact of CLL and its treatment on aspects of Health-Related Quality of Life in a population-based setting

The nationwide variation in trends in incidence, age-distribution, initial treatment and survival of patients with CLL is presented in chapter 2.1. In chapter 2.2, the magnitude of underreporting of CLL, and its underestimating effects on incidence rates, stage distribution, time to treatment and survival rates, are described.

In chapter 3.1 an in depth overview is given on the standardized incidence risks of CLL as a second primary malignancy, making a distinction between synchronic and metachronic cases. The case-study in Chapter 3.2 describes the epidemiology of CLL and T-cell lymphoma in one and the same patient and wonders about this coincidence is more than random.
The impact of active surveillance, chlorambucil and other therapy on Health-Related Quality of Life in patients with CLL is described in chapter 4.1

In the general discussion (chapter 5) the main results of these studies concerning several aspects of the burden of CLL are related to each other and put into perspective with the literature. An advice for future use of a population-based registry to explore the epidemiology, quality of life and best clinical practice for CLL patients is formulated.

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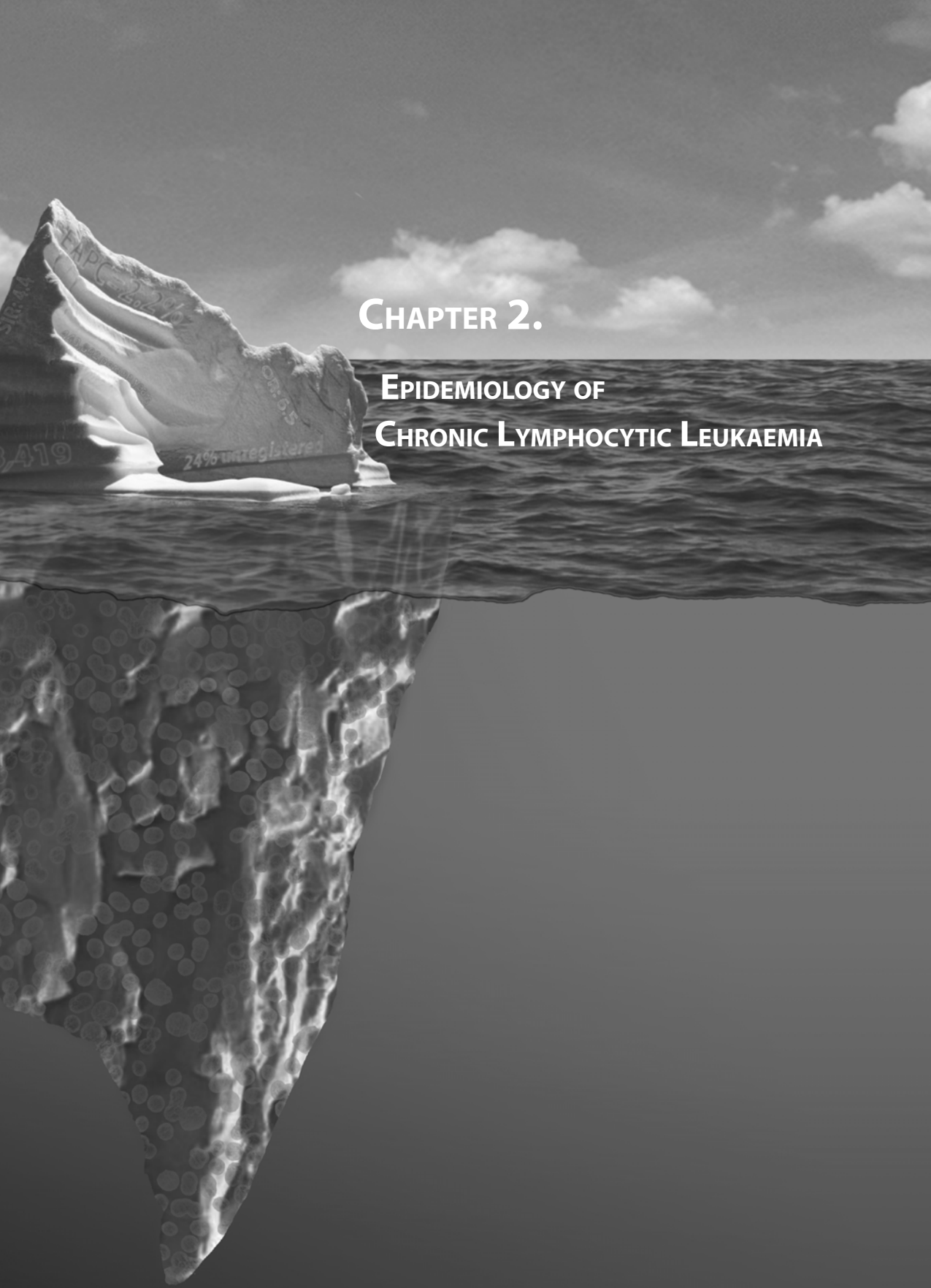
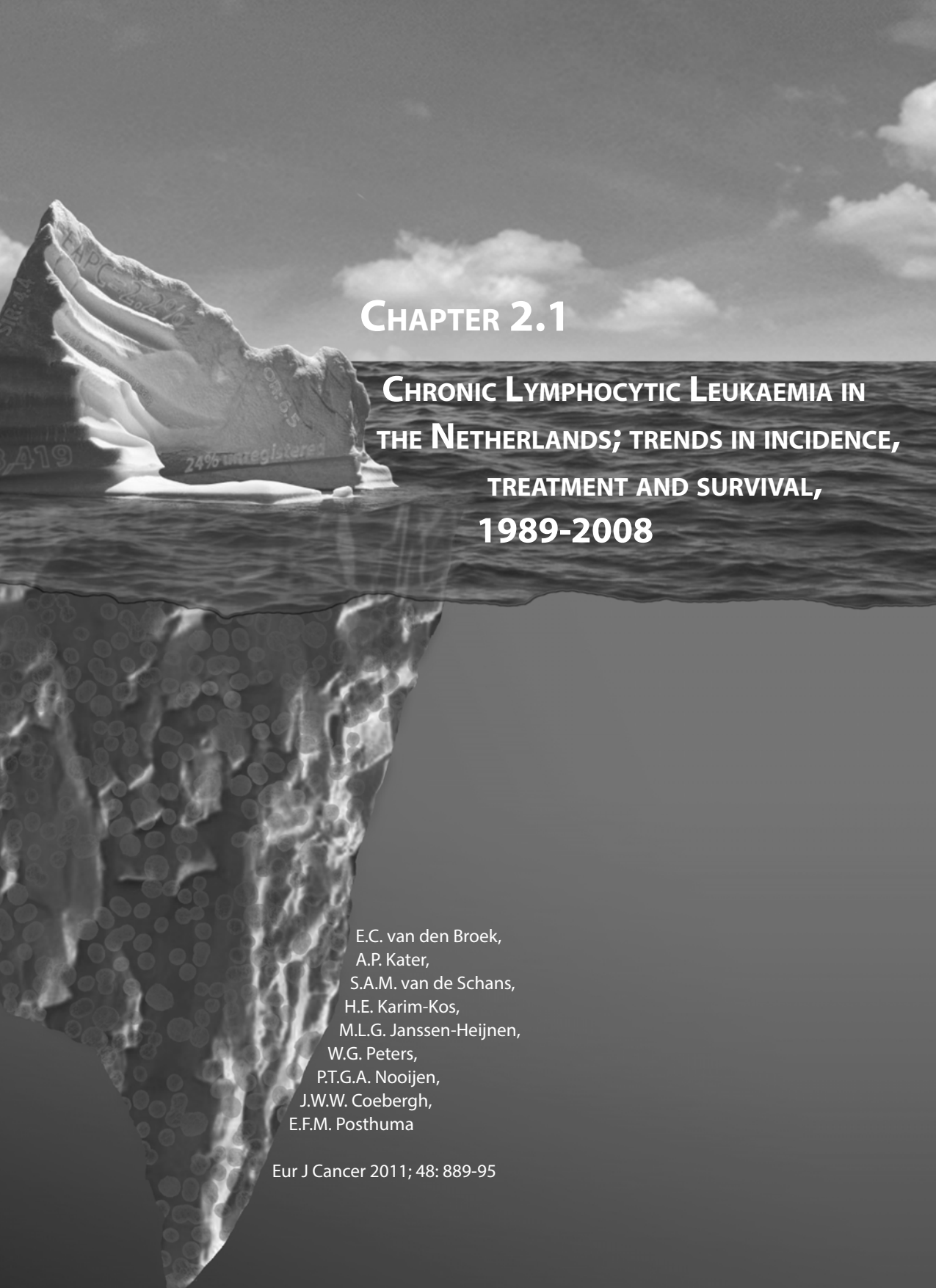


Chapter 2.

Epidemiology of Chronic Lymphocytic Leukaemia



Chapter 2.1

Chronic Lymphocytic Leukaemia in the Netherlands; trends in incidence, treatment and survival, 1989-2008

E.C. van den Broek,
A.P. Kater,
S.A.M. van de Schans,
H.E. Karim-Kos,
M.L.G. Janssen-Heijnen,
W.G. Peters,
P.T.G.A. Nooijen,
J.W.W. Coebergh,
E.F.M. Posthuma

Eur J Cancer 2011; 48: 889-95

Abstract

We present trends in incidence, early treatment and survival of Chronic Lymphocytic Leukaemia (CLL) between 1989 and 2008, based on population-based data from the Netherlands Cancer Registry.

Incidence rates were stable at 5.1 per 100,000 person-years for males, but increased from 2.3 to 2.5 for females, especially for females aged 50-64 years (from 3.6 to 4.3).

Patients were less likely to receive chemotherapy within six months, i.e. from 29% to 24% among males and from 25% to 21% among females. Five-year relative survival increased from 61% in 1989-1993 to 70% 2004-2008 for males, and from 71% to 76% for females. The relative excess risk of dying decreased in time to 0.7 (males) and 0.9 (females) in 2004-2008, reference 1989-1993, and increased with age to 2.9 (males) and 1.8 (females) in patients aged 75-94 years, reference 30-64 years.

The increasing incidence among females aged 50-64 coincided with the introduction of mass screening for breast cancer, which resulted in a large group of women under increased surveillance and possibly led to increased detection of CLL. The increase in survival might be underestimated due to possible decreased or delayed registration of indolent cases and the retroactive effect of the introduction of new therapies.

Introduction

Chronic Lymphocytic Leukaemia (CLL) is the most common type of Leukaemia in adults in western countries, both in terms of incidence and prevalence.[1] Median survival time is 10 years, ranging from months when the disease behaves aggressively, to decades for patients with an indolent course of the disease.[2]

The rising life expectancy of the Western population will lead to an increased number of patients with cancers that occur mainly in elderly patients, such as CLL (the incidence being 22 per 100,000 per year among people older than 65). [3] Furthermore, the incidence of CLL has been reported to be increasing among younger patients. [4] These two trends will lead to an increase in the prevalence.

Over the last decades, diagnostic tools have been refined, i.e. the use of flow cytometry to discriminate CLL from other lymphoproliferative disorders was gradually implemented since 1989, [5] leading to earlier detection and better discrimination between "true" CLL and its mild precursor Monoclonal B-Cell Lymphocytosis (MBL). [6]

Treatment options for patients with advanced disease have also changed. First, there was a breakthrough with the introduction of purine analogues such as fludarabine in the 1980s, followed by the introduction of monoclonal antibodies at the beginning of this century. [7, 8] Although response rates improved, randomized clinical trials (RCTs) comparing these newer treatments regimens failed to show improved overall survival, until recently. In 2010, a phase III study showed improvement of survival (three-year survival 87% versus 82%) after addition of a monoclonal antibody. [9]

Survival of the entire group of CLL patients might have already improved over the years coinciding the aforementioned developments, more therapeutic awareness, better supportive care and early detection. We therefore describe both long-term and recent trends in incidence, treatment and survival in a Western European, haematologically well-served country, using the Netherlands Cancer Registry.

Patients and Methods

The nationwide Netherlands Cancer Registry (NCR) was started in 1989 and is maintained and hosted by the regional cancer registries at eight regional Comprehensive Cancer Centres.[10] The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA), supplemented by notifications from the national registry of hospital discharge, various haematology and clinical chemistry laboratories and radiotherapy institutions. Information on patient characteristics such as gender and date of birth, tumour characteristics such as date of diagnosis and morphology (ICD-O-3) [11], and primary treatment are obtained routinely from the medical records six to twelve months after diagnosis.

Information on date of death was actively obtained from the municipal registries and from the database of deceased persons of the Central Bureau for Genealogy and the municipal

civil registries (GBA) (date of last follow-up: January 1st 2010). Survival time was calculated as the time from diagnosis to death or to 1 January 2010.

For the present study, all patients diagnosed with CLL (ICD-O-2 codes 9592 and 9803, ICD-O-2 / ICD-O-3 codes 9670, 9800, 9820, and 9823) in the period 1989-2008, aged 30 and over and recorded in the Netherlands Cancer Registry (NCR) were included (*N*=13,419). Age at diagnosis was divided into three groups (30-64, 65-74, and ≥75 years). Incidence rates were also calculated for the populations 30-49 years and 50-64 years. The study period was divided into four categories: 1989-1993, 1994-1998, 1999-2003, and 2004-2008. For the period 1989-1994 survival data from only five out of eight regional cancer registries was available, but were considered representative for the whole of the Netherlands. Patients older than 95 years at diagnosis were excluded from survival analysis (since follow-up is less reliable for this subgroup).

Annual incidence rates for the period 1989-2008 were calculated per 100,000 person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardised to the European standard population (European Standardised Rates (ESR)). Incidence rates were also calculated according to gender and age group. Trends in incidence were evaluated by calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence interval (95% CI). To calculate this, a regression line was fitted to the natural logarithm of the rates, using the calendar year as regressor variable (i.e. y=ax + b where y=ln (rate) and x=calendar year, then EAPC=100 * (e^a – 1)).

Treatment was described as the proportion patients who received no therapy, chemotherapy (whether or not combined with other kinds of therapy) or other therapy in the first six months after diagnosis. Detailed information on type of systemic therapy was not available until 2007.

Traditional cohort-based analysis was applied to calculate relative survival rates for patients diagnosed during 1989-2008. Since follow-up was available until January 2010, 10-year relative survival of patients diagnosed in the period 1999-2003 and the 5- and 10-year relative survival for patients diagnosed in the period 2004-2008 could not be calculated with the cohort-based method. To estimate these relative survival rates we used period-based relative survival analysis.[12] Multivariate relative survival analyses, using Poisson regression modelling [13], were carried out to estimate relative excess risk (RER) of dying adjusted for the follow-up interval and age category. We stratified for gender because effect modification was observed. SAS software (SAS system 9.2, SAS Institute, Cary, NC) was used to perform the statistical analyses.

Results

The distribution over the age categories was stable in males (*P*=0.09), with ~36% aged 30-64, ~34% aged 65-74 and ~30% aged 75 or older. In females a shift towards the youngest age category was seen, from 24% aged 30-64 in 1989-1993 to 32% in 2003-2008 (*P*=0.00). (Table 1)

Table 1: *Age, sex and subclassification distribution of CLL patients in the Netherlands, 1989-2008*

	Males				Females			
	'89-'93 *N* (%)	'94-'98 *N* (%)	'99-'03 *N* (%)	'04-'09 *N* (%)	'89-'93 *N* (%)	'94-'98 *N* (%)	'99-'03 *N* (%)	'04-'09 *N* (%)
Age								
30-64	567 (35%)	690 (35%)	791 (38%)	850 (37%)	279 (24%)	311 (24%)	476 (32%)	495 (32%)
65-74	541 (33%)	705 (36%)	707 (34%)	729 (32%)	371 (32%)	426 (34%)	398 (27%)	415 (27%)
≥75	507 (31%)	565 (29%)	606 (29%)	695 (31%)	526 (45%)	533 (42%)	608 (41%)	628 (41%)
Morphology code								
9592	89 (6%)	59 (3%)	30 (1%)	0 (0%)	74 (6%)	47 (4%)	18 (1%)	0 (0%)
9670	114 (7%)	242 (12%)	339 (16%)	424 (19%)	90 (8%)	151 (12%)	279 (19%)	377 (25%)
9800	30 (2%)	26 (1%)	10 (<1%)	0 (0%)	18 (2%)	29 (2%)	14 (1%)	3 (<1%)
9803	4 (<1%)	3 (<1%)	2 (<1%)	0 (0%)	2 (<1%)	2 (<1%)	0 (0%)	0 (0%)
9820	2 (<1%)	3 (<1%)	10 (<1%)	3 (<1%)	4 (<1%)	1 (<1%)	5 (<1%)	1 (<1%)
9823	1376 (85%)	1627 (83%)	1713 (81%)	1847 (81%)	988 (84%)	1040 (82%)	1166 (79%)	1157 (75%)

For all age groups together, the overall incidence rate (3.8 per 100,000 person years) and the incidence rate for males (5.1 per 100,000 person-years) were stable, whereas among females it increased slightly from 2.3 in 1989 to 2.5 per 100,000 person-years in 2008 (EAPC=0.8%; 95% CI: 0.1-1.6).

In the population 30-64 years, the incidence rate increased from 3.7 to 3.9 per 100,000 person-years (EAPC=0.6%; 95% CI: 0.1-1.1) for males and from 1.6 to 2.1 per 100,000 person-years (EAPC=2.2%; 95% CI: 0.7-3.7) for females. (Results not shown) Additional analysis of the populations aged 30-49 and 50-64 revealed that the increase in incidence for females was entirely attributable to an increase in the population aged 50-64 years, where the incidence rose from 3.6 to 4.3 per 100,000 person-years (EAPC=2.1%; 95% CI: 0.4-3.8). (Fig. 1a)

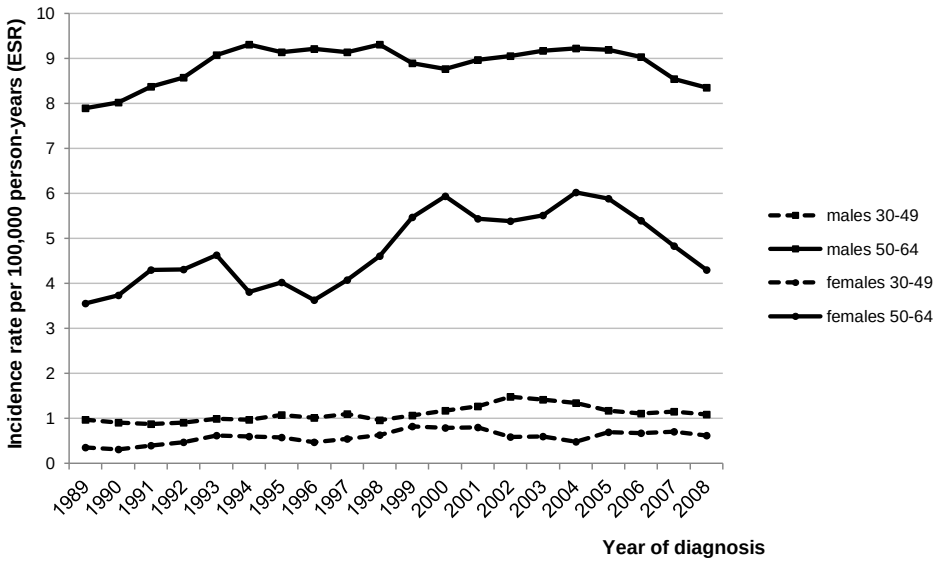


Figure 1a: *Three-year moving average of age-standardised incidence rates (ESR) of CLL in the Netherlands 1989-2008 according to gender, for patients aged 30-49 years and 50-64 years at diagnosis*

For patients aged 65-74 the incidence rates were stable around 24 and 12 per 100,000 person-years for males and females, respectively. In the population aged 75 and older the rates were stable around 36 and 19 per 100,000 person-years, respectively. (Fig. 1b)

The proportion of newly diagnosed patients treated with chemotherapy within six months after diagnosis decreased from 29% to 24% for males and from 25% to 21% for females, remaining higher for males in all age groups (results not shown) and periods. (Figure 2)

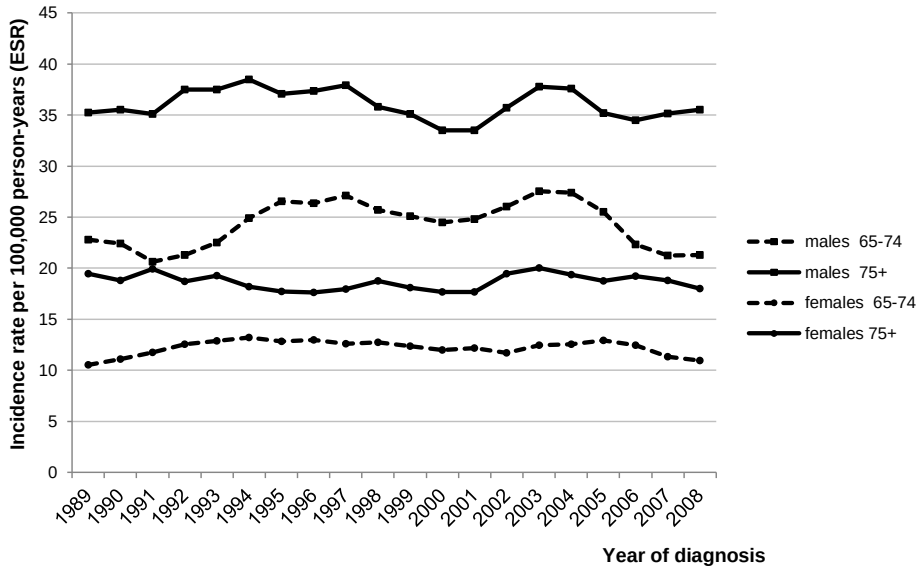


Figure 1b: *Three-year moving average of age-standardised incidence rates (ESR) of CLL in the Netherlands 1989-2008 according to gender, for patients aged 65-74 years and 75+ years at diagnosis*

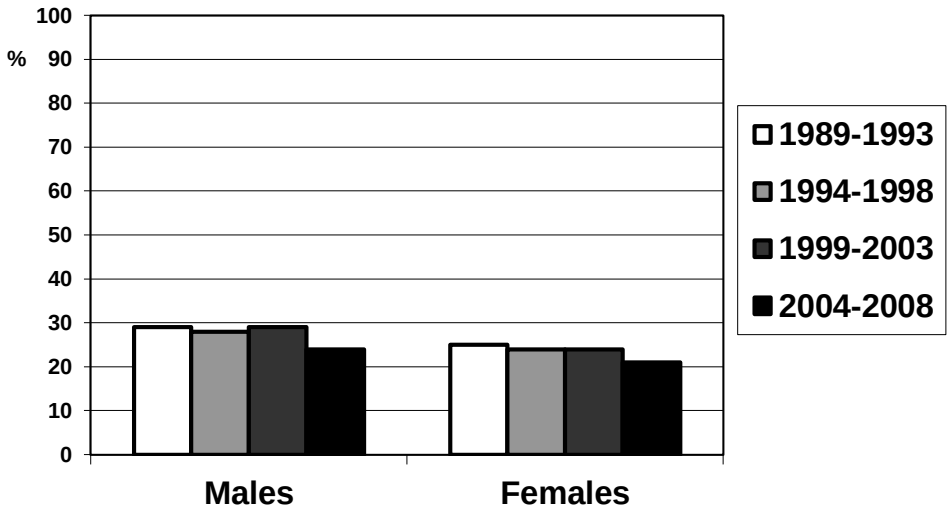


Figure 2: *Proportion of patients treated with chemotherapy within six months of diagnosis, in the Netherlands, according to age, gender and period*

For males, one-year survival increased from 86% in 1989-1993 to 91% 2004-2008 and three-year survival from 73% to 81%. Five-year survival went from 61% to 70%, ten-year survival was stable around 45%. For females, one-year survival remained stable around 90%, three-year survival increased from 81% to 85%, five-year survival went from 71% to 76% and

ten-year survival from 51% to 59%. Five- and ten-year survival rates for 2004-2008 were estimated with period analysis. Relative survival decreased with rising age at diagnosis, but was higher for females than for males at almost all times and in all age categories. (Table 2)

Table 2: *Relative survival rates (standard error) for CLL patients according to gender and period of diagnosis, the Netherlands*

Males					
Age group	**Survival rate after year**	**1989-1993**	**1994-1998**	**1999-2003**	**2004-2008**
All	1	86.4 (1.1)	88.0 (0.9)	89.7 (0.8)	91.1 (0.7)
	3	72.8 (1.5)	77.0 (1.2)	78.4 (1.1)	80.7 (1.1)
	5	60.6 (1.8)	65.5 (1.4)	67.8 (1.3)	69.5* (1.3)
	10	43.5 (2.0)	43.4 (1.6)	47.5* (1.8)	44.9* (1.6)
30-64	1	92.9 (1.2)	92.1 (1.1)	96.5 (0.7)	95.2 (0.8)
	3	83.2 (1.9)	84.6 (1.5)	88.6 (1.3)	89.1 (1.3)
	5	71.4 (2.3)	76.2 (1.8)	80.1 (1.6)	79.5* (1.5)
	10	51.2 (2.6)	54.3 (2.2)	59.6* (2.4)	55.5* (2.0)
65-74	1	87.5 (1.8)	90.6 (1.3)	90.7 (1.3)	91.8 (1.2)
	3	70.6 (2.6)	78.5 (2.0)	79.8 (1.9)	79.9 (1.9)
	5	56.1 (3.0)	63.5 (2.4)	66.0 (2.2)	65.5* (2.1)
	10	43.2 (3.7)	36.0 (2.6)	44.0* (3.1)	37.0* (2.5)
75-95	1	76.6 (2.6)	78.7 (2.2)	78.4 (2.1)	84.6 (1.8)
	3	61.1 (3.6)	63.2 (3.0)	60.8 (2.8)	69.9 (2.8)
	5	50.8 (4.3)	51.5 (3.6)	50.0 (3.2)	58.8* (3.3)
	10	30.8 (6.1)	36.5 (5.2)	31.8* (5.5)	36.4* (5.0)
Females					
Age group	**Survival rate after year**	**1989-1993**	**1994-1998**	**1999-2003**	**2004-2008**
All	1	89.6 (1.2)	88.6 (1.1)	90.7 (0.9)	91.4 (0.8)
	3	80.6 (1.6)	80.2 (1.4)	81.5 (1.3)	84.9 (1.2)
	5	71.4 (1.9)	72.7 (1.7)	73.5 (1.5)	76.3* (1.5)
	10	51.2 (2.3)	55.3 (2.1)	55.9* (2.2)	58.5* (1.9)
30-64	1	97.1 (1.2)	95.5 (1.3)	97.3 (0.8)	98.0 (0.7)
	3	90.2 (2.1)	92.2 (1.7)	90.4 (1.5)	92.9 (1.4)
	5	82.3 (2.7)	86.2 (2.2)	83.5 (1.9)	85.2* (1.8)
	10	57.6 (3.5)	72.0 (2.9)	66.8* (3.1)	71.3* (2.4)
65-74	1	95.8 (1.4)	95.1 (1.2)	92.0 (1.5)	95.8 (1.1)
	3	89.7 (2.2)	85.0 (2.1)	82.3 (2.2)	88.6 (2.0)
	5	78.8 (2.9)	75.5 (2.6)	75.9 (2.6)	80.8* (2.4)
	10	56.9 (3.8)	56.9 (3.3)	56.8* (3.4)	58.7* (3.3)
75-95	1	80.6 (2.3)	78.9 (2.1)	84.1 (1.8)	82.6 (1.8)
	3	67.8 (3.1)	68.0 (2.8)	73.1 (2.5)	75.0 (2.6)
	5	58.9 (3.7)	61.1 (3.4)	62.5 (3.0)	64.9* (2.9)
	10	44.5 (5.4)	40.0 (4.6)	45.0* (5.2)	45.1* (4.4)

* = *estimation based on period-analysis*

The relative excess risk of dying decreased in time to 0.7 and 0.9 in 2004-2008, males and females respectively, reference 1989-1993, and increased with age to 2.9 and 1.8 in patients aged 75-94 years, males and females respectively, reference 30-64 years (Table 3)

Table 3: *Relative excess risk of dying for CLL patients in the Netherlands*

	Variable	RER	95% CI
Males	**Period of diagnosis**		
	1989-1993	1	
	1994-1998	0.8*	0.7-1.0
	1999-2003	0.8*	0.7-0.9
	2004-2008	0.7*	0.6-0.8
	Age group (years)		
	30-64	1	
	65-74	1.8*	1.6-2.0
	75-94	2.9*	2.6-3.3
Females	**Period of diagnosis**		
	1989-1993	1	
	1994-1998	0.8	0.5-1.3
	1999-2003	0.6	0.4-1.1
	2004-2008	0.9	0.4-1.8
	Age group (years)		
	30-64	1	
	65-74	1.3	0.8-2.1
	75-94	1.8*	1.1-3.0

**) P <0.05*

Multivariate relative survival analyses, using Poisson regression modelling, to estimate relative excess risk (RER) of dying adjusted for follow-up interval.

Discussion

In this study with unselected data on CLL diagnosed in the entire Netherlands over a period of 20 years, we saw an increase in incidence for females aged 50-64 years (from 3.6 to 4.3 per 100,000 person-years). The proportion of patients receiving chemotherapy within six months decreased and survival rates increased modestly.

The overall age standardised incidence rate of 3.8 per 100,000 was in accordance with European data. [14] A paper on trends in incidence in the USA from 1987 – 2001 also reported a stable incidence rate. [15] In Denmark an increase in incidence was seen between 1943 and 2003. [16] If we leave the Danish data before 1989 out of consideration, we see trends similar to our findings.

For patients younger than 65 years, we saw an increase in incidence, that was most pronounced among middle-aged women (50-65 years), which might be explained by higher detection levels following the gradual implementation of the breast cancer screening program in The Netherlands starting in 1990. This resulted in an increase in breast cancer survivors, [17] who undergo frequent medical check ups that could expose CLL coincidentally. The decrease in incidence among females aged 50-64 between 2004-2008 is another indication for increased detection among this group. Because of CLL's long subclinical phase, detecting all patients at a certain period at a subclinical phase, will cause a increase in incidence, which will be followed by a decline, as all the cases that would be detected as the patient presented with symptoms are already diagnosed.
The higher use of health care services among middle-aged women [18], could also have led to increased detection in this group.

Some of the fluctuations in the incidence rates in males showed similarities with fluctuations in the incidence of prostate cancer, [19] leading us to assume increased detection among cancer survivors might be of influence here too.

Men received systemic therapy more often than women in the first half year after diagnosis, suggesting that women were diagnosed with early-stage disease more often, as was seen in previous studies. [20]

A decreasing proportion of patients was treated within six months after diagnosis. Physicians may have become more hesitant about systemic therapy. International guidelines for indications for treatment have not changed essentially, however there was a trend toward stronger in discouragement of treatment of indolent patients without active disease. [21-23] Another explanation is that diagnoses may have been set earlier and at a more indolent stage. This is consistent with the shift towards younger age at diagnosis we observed.

A stage shift towards earlier stages could also explain the increasing survival rates, in the absence of life-prolonging therapies. A decreasing trend was visible in excess risk of dying; however not statistically significant for females, probably due to the small number of patients.

As, up to recently, few trials showed improvement in survival as a result of anti-cancer treatment,[24] the improvement in survival in our study might have resulted from earlier detection and/or better supportive care rather than improved systemic treatment.

In most age categories and periods, relative survival rates appeared to be higher for females than for males. In other studies this was suggested to be attributable to better longevity of women. [20] However, our relative survival rates were age and gender-adjusted, so there should be another reason. As mentioned earlier, men might be diagnosed more often with advanced stage disease than women or they may suffer more comorbidities. A first analysis of the comorbidities in a subset of the population showed that male CLL patients did not present more often with comorbidities in general, but they did suffer more often from life-threatening cardiovascular diseases.

The difference in survival between males and females decreased. In the USA and Sweden higher relative survival rates for females and trends toward smaller gender differences were also observed.[4 25] In Barcelona, stable survival rates for females and increased survival rates for males were observed, as well as stable rates for patients with Binet stage A and increased rates in patients with stage B/C. [2] If men are diagnosed more often in a later stage, this could clarify why they benefit more from developments in treatment than women. It also explains why the presumed higher detection rates for middle-aged women did not result in marked improvement of survival.

The significantly higher relative excess risk of dying of older patients was also in line with the American and Swedish data. [4 25]

We should consider several limitations of this analysis: The basis for the diagnostic criteria for CLL changed from absolute lymphocyte count (ALC) towards B-cell count. A single centre study showed that 42% of the patients, who would be classified as having Rai stage 0 CLL according to their ALC, would be classified as having MBL using B-cell count, [26] i.e. the proportion of patients with a good prognosis decreased. However, since the guidelines did not recommend the use of B-cell count until 2008, [27] the influence on the data presented in this article was probably limited.

Furthermore, cancer registries could always rely on pathology reports to signal new CLL cases, but the introduction of flow cytometry changed this. Before, a bone marrow or lymph node biopsy was performed to confirm the primary diagnosis of CLL. Currently, these biopsies are only indicated in case of doubt of the diagnosis, when transformation to Richter's disease is suspected or in case of cytopenia. As a result, a substantial number of CLL cases will not be recorded in the cancer registries, causing underestimation of the incidence [28] and stressing the necessity for cancer registries to adapt their approach to CLL registration. If underreporting concerns mainly indolent cases, then underestimation of the survival rates would follow.

Third, for the present study, ICD-O-2 codes 9592 and 9803, ICD-O-2 / ICD-O-3 codes 9670, 9800, 9820, and 9823 were used to select patients with CLL/SLL. Not all codes indicate CLL

or SLL specifically. 9592, 9800, 9803 and 9820 are more generic. The NCR has reviewed all patients that were recorded after 1999 with generic codes, and replaced these codes by more specific codes if the source provided sufficient information. It appeared that most cases concerned CLL, hence the cases that were not recoded (either because the diagnoses was before 2000 or the source did not provide enough details) were classified as CLL/SLL [29] To discard cases with these non-specific codes that are probably not CLL patients, we excluded patients that were younger than 30 at time of diagnosis (N=27).

Finally, since the time-to-therapy can be many years for CLL patients, the introduction of new therapies has a retroactive effect; previously diagnosed patients also benefit from it upon disease progression, resulting in a less steep increase of survival rates.

In conclusion, the gender differences in the incidence of CLL remained but became smaller. The incidence rate for females increased towards the stable incidence rate for males, probably due to increased detection rates in women. The modest increase in survival is possibly underestimated as a result of underregistration of recently diagnosed indolent cases and the retroactive effect of the introduction of new therapies.

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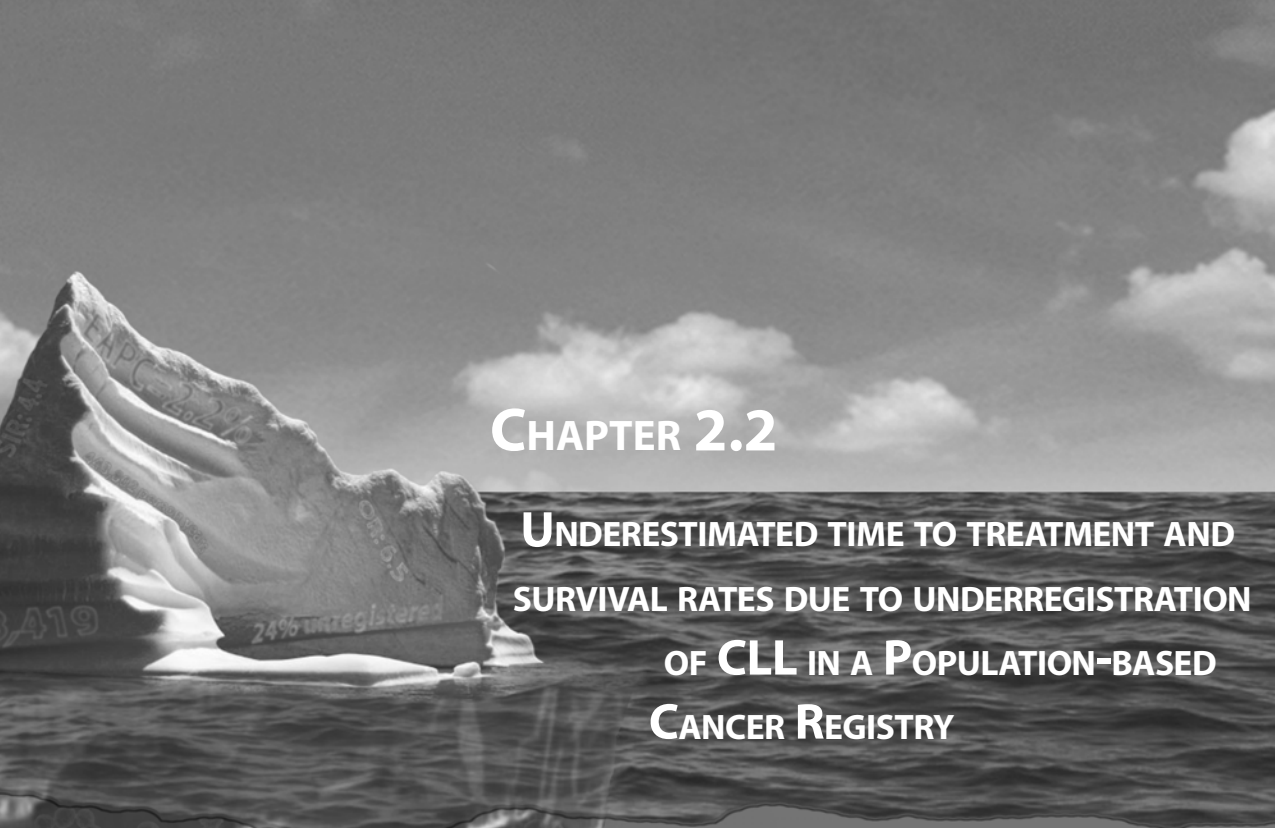

Chapter 2.2

Underestimated time to treatment and survival rates due to underregistration of CLL in a Population-based Cancer Registry

E.C. van den Broek,
W.G. Peters,
V. Scharnhorst,
A. Koster,
E.F.M. Posthuma,
J.W.W. Coebergh,
L.V. van de Poll-Franse

Submitted for publication

Abstract

The introduction of new therapies for Chronic Lymphocytic Leukaemia (CLL) and changing treatment paradigms, make complete population-based data more crucial than before. Complete registration is threatened as pathological confirmation and hospitalizations are often lacking.

We reviewed 482 patients who were tested and/or treated for CLL in 2009 in two hospitals, and found that 117 (24%) CLL cases were not yet registered in the ECR. After addition of the unregistered patients, the proportion of patients with Rai 0 CLL increased from 59% to 67% ($p < 0.001$). Registered Rai 0 patients had a 5-year survival of 76% versus 90% for unregistered Rai 0 patients. Five year after diagnosis, 61% of the registered patients had not started therapy versus 93% of the unregistered patients.

Underregistration obstructs proper etiological research and health resource planning and can have an unfavourable influence on treatment choice.

Introduction

Population-based cancer registry data form a widely used source to calculate the extent of the cancer burden in a population, follow trends in incidence, treatment and survival and enables establishment of public health priorities. Hence, completeness is desired and representativity is absolutely indispensable.

To ensure the completeness, the Eindhoven Cancer Registry (ECR) collects cancer cases through several ways. First of all, there is a notification of all newly diagnosed malignancies in the Netherlands by the Dutch Pathology Registry (PALGA)[1] on a regular basis. This is supplemented by notifications from the national registry of hospital discharge and radiotherapy institutions. In some of the hospitals the haematology and clinical chemistry laboratories provide cases. As most cancers require pathological confirmation as well as one or more hospitalizations, this approach leads to an estimated completeness of at least 95%.[2]

However, Chronic Lymphocytic Leukaemia (CLL) is not like most cancers. Unlike the majority of other malignancies, the definite diagnosis of CLL does not require pathological confirmation. It can be made by flow cytometric analysis of a blood sample in clinical chemical laboratories.[3] Currently, biopsies are only indicated in case of doubt of the diagnosis, when transformation to Richter's disease is suspected or in case of cytopenia.[4]

In addition, most CLL patients do not require treatment for their disease at the time of diagnosis and the disease can be managed without hospitalizations.[3] Hospitalization may be only required in case of severe symptoms and/or the necessity to start therapy.

As a consequence, many (mainly asymptomatic early-stage) CLL-cases are signalled by neither the pathology reports nor the hospital records. This poses a potential threat for complete cancer registration, which can not only result in an underestimation of the incidence[5], but also in incorrect information on stage distribution and an underestimation of the survival rates. Currently, many new promising yet expensive therapies are (about to be) introduced and the treatment paradigms are about to change.[6 7] This makes representative population-based data more crucial than before.

In this paper, we establish the extent of underreporting of CLL in the ECR, and describe the consequences for the estimated stage distribution and survival rates. We hypothesized the underregistration to be about 30%, which would be similar to other cancer registries with a comparable mode of operation. [5, 8] Additionally, we hypothesized that recalculation, after inclusion of all previously unregistered cases, would result in a more favourable stage distribution with a higher proportion of Rai 0 patients and better survival rates for the entire population as well as per risk category.

Methods

Data Collection

By using the administrative codes upon which the Dutch hospital funding system is based, we retrieved patient data from all patients in two hospitals who were tested and/or treated for CLL in 2009 (both incident and prevalent cases). From one of those hospitals

we additionally retrieved patient data of patients in whose blood a monoclonal B-cell population with the immune phenotype CD5, CD19 and CD23 positive was found, which suggests presence of CLL. First, we verified whether the patient was registered in the ECR. The files from unregistered patients were reviewed and patients were additionally registered in the ECR retrospectively, if applicable (e.g. patients with monoclonal B-cell lymphocytosis are not registered in the ECR).

For patients newly diagnosed in 2004 or later, additional data were collected within the scope of the Population-based HAematological Registry for Observational Studies (PHAROS; www.pharosregistry.nl). PHAROS is a supplement to the Netherlands Cancer Registry (NCR), of which the ECR is a part of.

Statistical Analyses

Patients diagnosed in 2004 or later, for whom additional PHAROS data were collected, were included in the analyses. Patient characteristics were described according to registration status (already registered in ECR vs. previously unregistered). Differences between the two groups were tested with chi-square analyses. Survival was defined as the time between date of diagnosis and date of death or 1 January 2012 for the patients who were still alive. The Log-Rank-test was used to compare univariable survival rates between registered and unregistered patients in the ECR for the entire population as well as the patients with Rai 0 CLL solely. Time to first treatment was defined as the time between date of diagnosis and date of first administration of chemo-and/or immunotherapy or end of follow-up for untreated patients.

A multivariable proportional hazards regression analysis was performed to discriminate independent risk factors for both death and treatment. The proportional hazard assumption of the predictor was evaluated by applying Kaplan-Meier Curves.
All statistical analyses were performed using SAS (version 9.3 for Windows; SAS Institute Inc., Cary, NC). P values of <.05 were considered statistically significant.

Results

After reviewing 482 potential CLL-cases extracted from administrative or laboratory database, we found that 117 (24%) CLL cases and 14 cases of other haematological malignancies were not yet registered in the ECR. (Figure 1) The unregistered patients were statistically significantly more often diagnosed with Rai 0 CLL. ($p < 0.001$) After addition of the unregistered patients the proportion of patients with Rai 0 CLL increased from 59% to 67% ($p < 0.001$). Furthermore, unregistered patients were diagnosed in more recent years. No statistically significant differences were found for sex, age at diagnosis and number of comorbidities between registered and unregistered patients (Table 1).

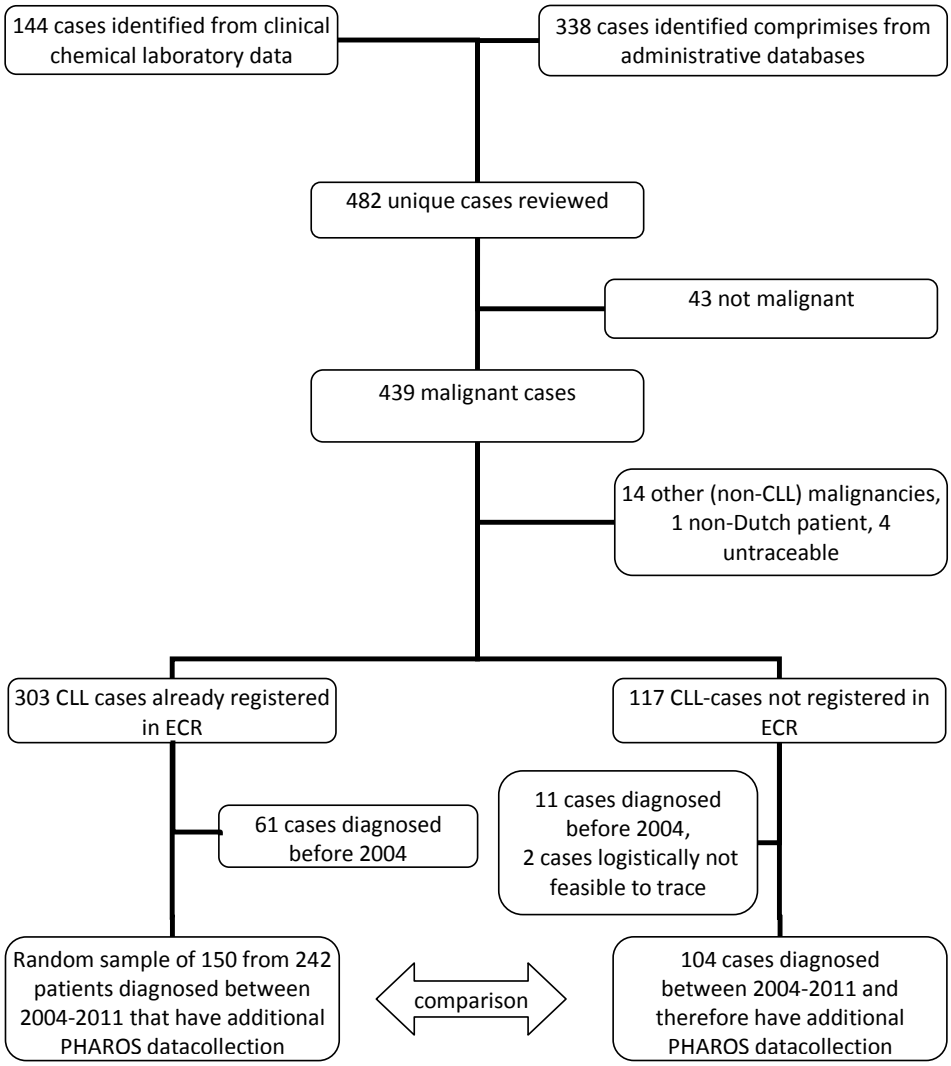

Figure 1: *Flow chart of CLL identification and registration based on laboratory, administrative (DBC codes) and cancer registry extraction in 2 hospitals in the period 2004-2011*

Table 1: *Sociodemographic and clinical characteristics of patients with CLL according to registration status in the Eindhoven Cancer Registry*

	Total (N=254)		Registered (N=150)		Unregistered (N=104)		
	N	**%**	**N**	**%**	**N**	**%**	**p-value**
Sex							0.17
male	161	63%	101	67%	60	58%	
female	93	37%	49	33%	44	42%	
Age, mean	67.6		66.6		69.0		0.14
<50	17	7%	14	9%	3	3%	
50-65	79	31%	49	33%	30	28%	
65-75	86	34%	49	33%	37	36%	
75+	72	28%	38	25%	34	33%	
Year							<0.01
2004	30	12%	24	16%	6	6%	
2005	35	14%	27	18%	8	8%	
2006	29	11%	16	11%	13	13%	
2007	27	11%	19	13%	8	8%	
2008	35	14%	20	13%	15	14%	
2009	52	20%	24	16%	28	27%	
2010	38	15%	18	12%	20	19%	
2011	8	3%	2	1%	6	6%	
Rai stage							<0.01
0	170	67%	88	59%	82	79%	
1	34	13%	21	14%	13	13%	
2	26	10%	19	13%	7	7%	
3	12	5%	11	7%	1	1%	
4	12	5%	11	7%	1	1%	
Comorbidities							0.9
0	74	29%	45	30%	29	28%	
1	86	34%	48	32%	38	37%	
2	84	33%	51	34%	33	32%	
9	10	4%	6	4%	4	4%	

Survival time of the unregistered patients appeared to be longer (p<0.01) compared to registered patients and of all patients combined (Figure 2A). Unregistered patients had a 5-year survival of 90%, whereas registered patients had a 5-year survival of 72%. The 5-year survival of all these patients combined, resulted in an actual survival of 78% for CLL-patients.

Additional subgroup analyses revealed that the survival time of the unregistered Rai 0 patients was also higher than that of registered Rai 0 patients, although this difference did not reach statistical significance (p=0.06) (Figure 2B). Unregistered Rai 0 patients had a 5-year survival of 90% (the difference with the entire group of unregistered patients was marginal, as this group consisted almost completely of Rai 0 patients), whereas registered Rai 0 patients had a 5-year survival of 76%.

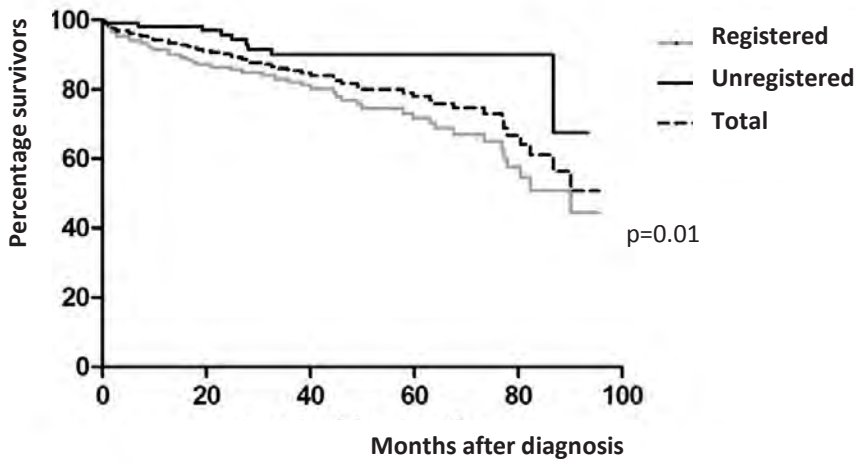

Figure 2A: *Survival of all CLL-patients registered (n=150) and unregistered (n=104) in the Eindhoven Cancer Registry*

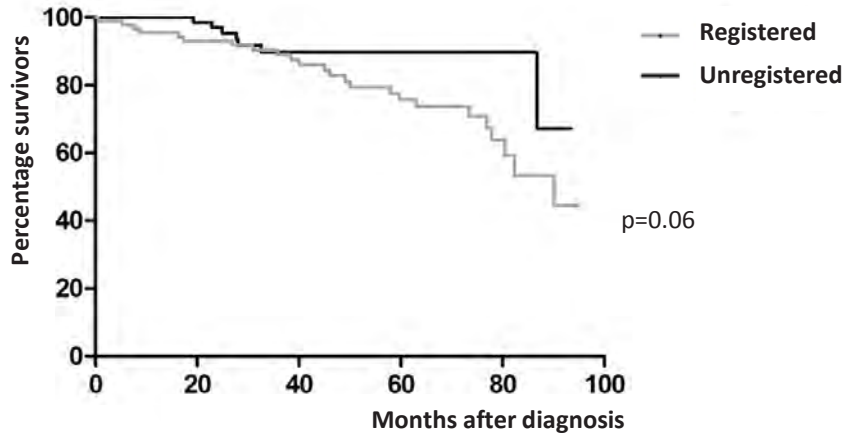

Figure 2B: *Survival of Rai 0 CLL-patients registered (n=88) and unregistered (n=82) in the Eindhoven Cancer Registry*

Cox regression analyses comparing overall mortality between registered and unregistered patients , taking into account differences in gender, age, year of diagnosis and stage at diagnosis showed a hazard ratio (HR) of 0.4 (95% confidence interval (CI) 0.2-0.8). Again, subgroup analyses including Rai 0 patients only, showed similar results with a HR for overall mortality being 0.4 (95% CI: 0.2-0.9) for unregistered versus registered patients after correction for gender, age at diagnosis and year of diagnosis (Table 2). However, the predictor did not satisfy the assumption of proportionality as the graphs of the survival function versus the survival time did not result in graphs with perfectly parallel curves, nor did the graphs of the log(-log(survival)) versus log of survival time.

Table 2: *Cox multivariate regression analysis of variables associated with overall mortality for patients with CLL*

		All patients			Rai 0 patients only		
Variable		**Hazard Ratio**	**(95% CI)**	**p-value**	**Hazard Ratio**	**(95% CI)**	**p-value**
Registered in ECR	yes	1.0			1.0		
	no	0.4	(0.2-0.8)	<0.01	0.4	(0.2-0.9)	0.03
Gender	male	1.0			1.0		
	female	0.5	(0.3-1.1)	0.07	0.4	(0.2-1.0)	0.04
Age at diagnosis	<50	0.2	(0.1-0.9)	0.04	0.2	(0.0-1.7)	0.15
	50-65	0.2	(0.1-0.4)	<0.01	0.2	(0.1-0.6)	<0.01
	65-75	0.4	(0.2-0.7)	<0.01	0.4	(0.2-0.9)	0.02
	>75	1.0			1.0		
Year of diagnosis		1.1	(0.9-1.3)	0.44	1.2	(1.0-1.6)	0.11
Stage at diagnosis	Rai 0	1.0					
	Rai 1-2	1.4	(0.7-2.7)	0.34			
	Rai 3-4	2.3	(1.0-4.9)	0.04			

ECR= Eindhoven Cancer Registry; CI=Confidence Interval

Time to first treatment of the unregistered patients appeared to be longer (p<0.01) compared to registered patients and of all patients combined. This was the case for both the entire patient group as well as the Rai 0 patients. (Figure 3A and 3B) Five year after diagnosis 61% of the registered patients had not started chemo- and/or immunotherapy versus 93% of the unregistered patients. For all these patients combined, the proportion of untreated patients five year after diagnosis was 73%.
From the registered Rai 0 patients, 77% had not started chemo- and/or immunotherapy compared to 97% of the unregistered patients. In the entire group of Rai 0 patients, the proportion untreated patients five year after diagnosis was 85%.

Cox regression analyses comparing treatment status between registered and unregistered patients , taking into account differences in gender, age, year of diagnosis and stage at diagnosis showed a hazard ratio (HR) of 0.2 (95% confidence interval (CI) 0.0-0.4). Again, subgroup analyses including Rai 0 patients only, showed similar results with a HR for treatment status being 0.3 (95% CI: 0.0-0.9) for unregistered versus registered patients after correction for gender, age at diagnosis and year of diagnosis (Table 3).

Evaluation of the proportional hazard assumption of the predictor by applying Kaplan-Meier Curves showed that the predictor satisfied the assumption of proportionality as the graphs of the survival function versus the survival time resulted in graphs with parallel curves as did the graphs of the log(-log(survival)) versus log of survival time.

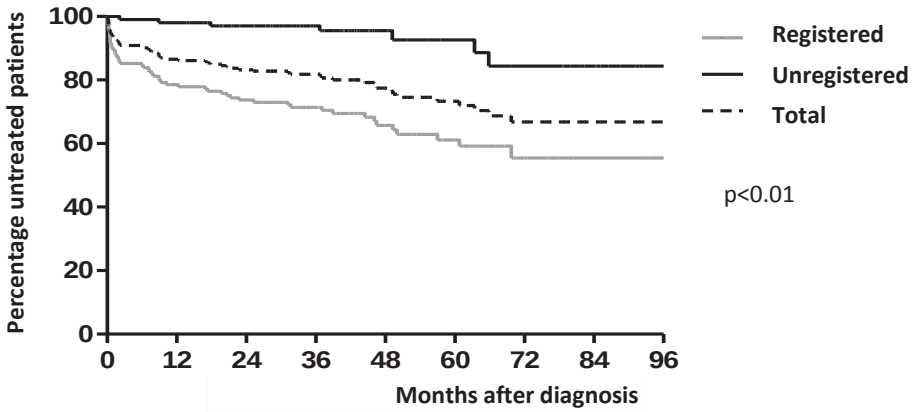

Figure 3A: *Proportion of untreated CLL-patients registered (n=150) and unregistered (n=104) in the Eindhoven Cancer Registry*

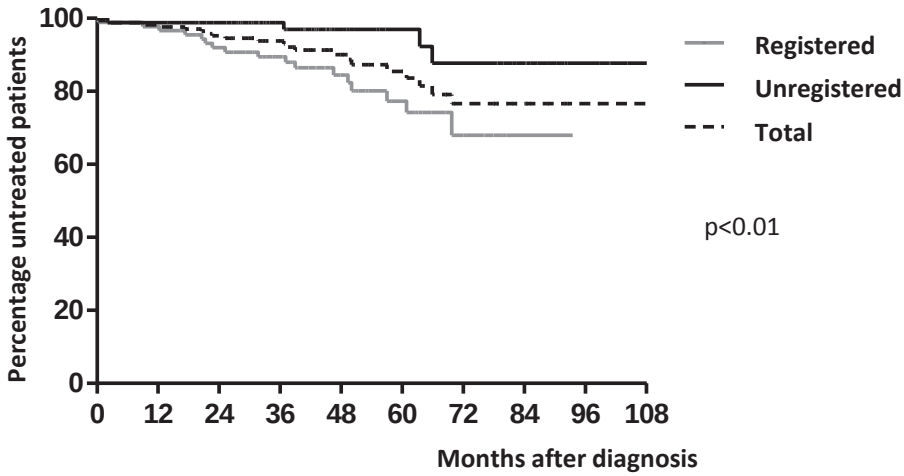

Figure 3B: *Proportion of untreated Rai 0 CLL-patients, registered (n=88) and unregistered (n=82) in the Eindhoven Cancer Registry*

Table 3: *Cox multivariate regression analysis of variables associated with treatment status for patients with CLL*

		All patients			Rai 0 patients only		
Variable		**Hazard Ratio**	**(95% CI)**	**p-value**	**Hazard Ratio**	**(95% CI)**	**p-value**
Registered in ECR	yes	1.0			1.0		
	no	0.2	(0.0-0.4)	<0.01	0.3	(0.0-0.9)	0.03
Gender	male	1.0			1.0		
	female	1.3	(0.8-2.4)	0.3	1.8	(0.7-4.5)	0.2
Age at diagnosis	<50	3.5	(1.3-9.1)	0.01	22.7	(1.9-274)	0.01
	50-65	1.2	(0.5-2.5)	0.7	3.4	(0.4-29.1)	0.27
	65-75	1.9	(0.9-3.9)	0.08	11.9	(1.5-92.0)	0.02
	>75	1.0			1.0		
Year of diagnosis		1.0	(0.9-1.1)	0.72	0.7	(0.5-1.0)	0.03
Stage at diagnosis	Rai 0	1.0					
	Rai 1-2	3.4	(1.9-6.4)	<0.01			
	Rai 3-4	15.7	(7.8-31.7)	<0.01			

ECR= Eindhoven Cancer Registry; CI=Confidence Interval

Discussion

In this study we observed a 24% underregistration of CLL patients in the Eindhoven Cancer Registry, slightly lower than the 27% in a Canadian cancer registry [8] and the 38% found in a U.S. tumour registry.[5]

Of the previously registered CLL-patients, 59% was diagnosed with Rai 0 CLL, thus patients with Rai 0 CLL increased to 67%. This is still lower than the earlier reported 80% reported in previous publications. [9, 10]

Underregistration resulted in an underestimation of 6% of the 5-year survival rate; after inclusion of the newly registered patients, the rate increased from 72% to 78%. This could not solely be explained by the larger proportion of Rai 0 patients, as we found similar results within this group of patients; newly registered Rai 0 patients had a 5-year survival of 90%, whereas previously registered Rai 0 patients had a 5-year survival of only 76%. The differences in the survival curves were not statistically significant, but we assume this is the result of a small patient population and relatively high survival rates.

Underreporting of haematological malignancies has been common among cancer registries. In 2012 underregistration of half of the Acute Myeloid Leukaemia cases and two thirds of the Chronic Myeloid Leukaemia cases occurred in the well financed Surveillance Epidemiology and End Results (SEER) database.[11] In Brazil, the completeness of the registration in population-based cancer registries of childhood Acute Lymphocytic Leukaemia varied from 16% to 35%. The underreporting of leukaemia and lymphoma in the Swedish Cancer registry was calculated to be 17%.[12] Underreporting of CLL and its consequences on survival rates were also described in the HAEMACARE project, but mainly for Eastern Europe.[13]

Unfortunately, documentation of the (un)representativity of the registered patients is scarce. We proved the impact on both the estimated incidence, as well as the estimated stage distribution and survival rates to be substantial.

Underregistration can lead to suboptimal health resource planning. In this particulate case, the unregistered patients will contribute little to the total treatment cost, as it concerns mainly asymptomatic early- stage CLL cases, with a long time to first treatment. However, as this group exhibits high survival rates, they will account for many more outpatient clinic visits than expected. The interval between the visits could also become shorter than necessary due to underestimation of time to first treatment.

Furthermore, underreporting obstructs proper etiological research. Currently, most epidemiological studies describe a stable or even declining incidence of CLL.[14,15] This could be true, but it could also be the result of an increasing incidence that is concealed due to increasing underreporting. If the latter is the case, CLL is not given the attention it should receive. Underestimated survival rates, especially within risk-groups, can have an unfavourable influence on treatment choice, as therapy can be started or abstained unnecessarily. Additionally, the treatment of choice could be less or more aggressive than desired.

In 2007, Linet et al. already recommended standardization of reporting of CLL across cancer registries, to identify all CLL cases completely and accurately.[16] We strongly support this recommendation and call all cancer registries to critically review their methods of case collection to ensure complete and representative data.

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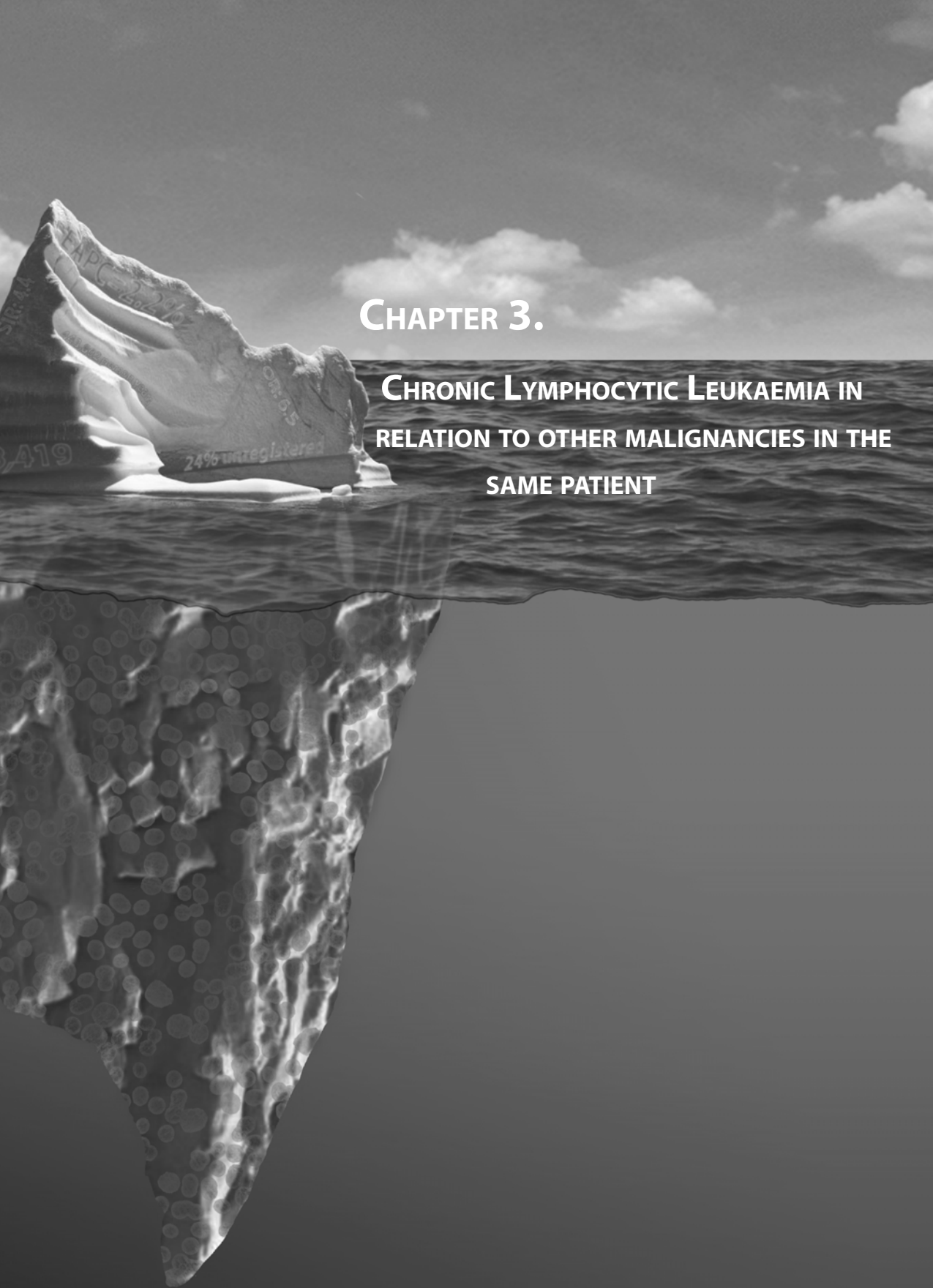
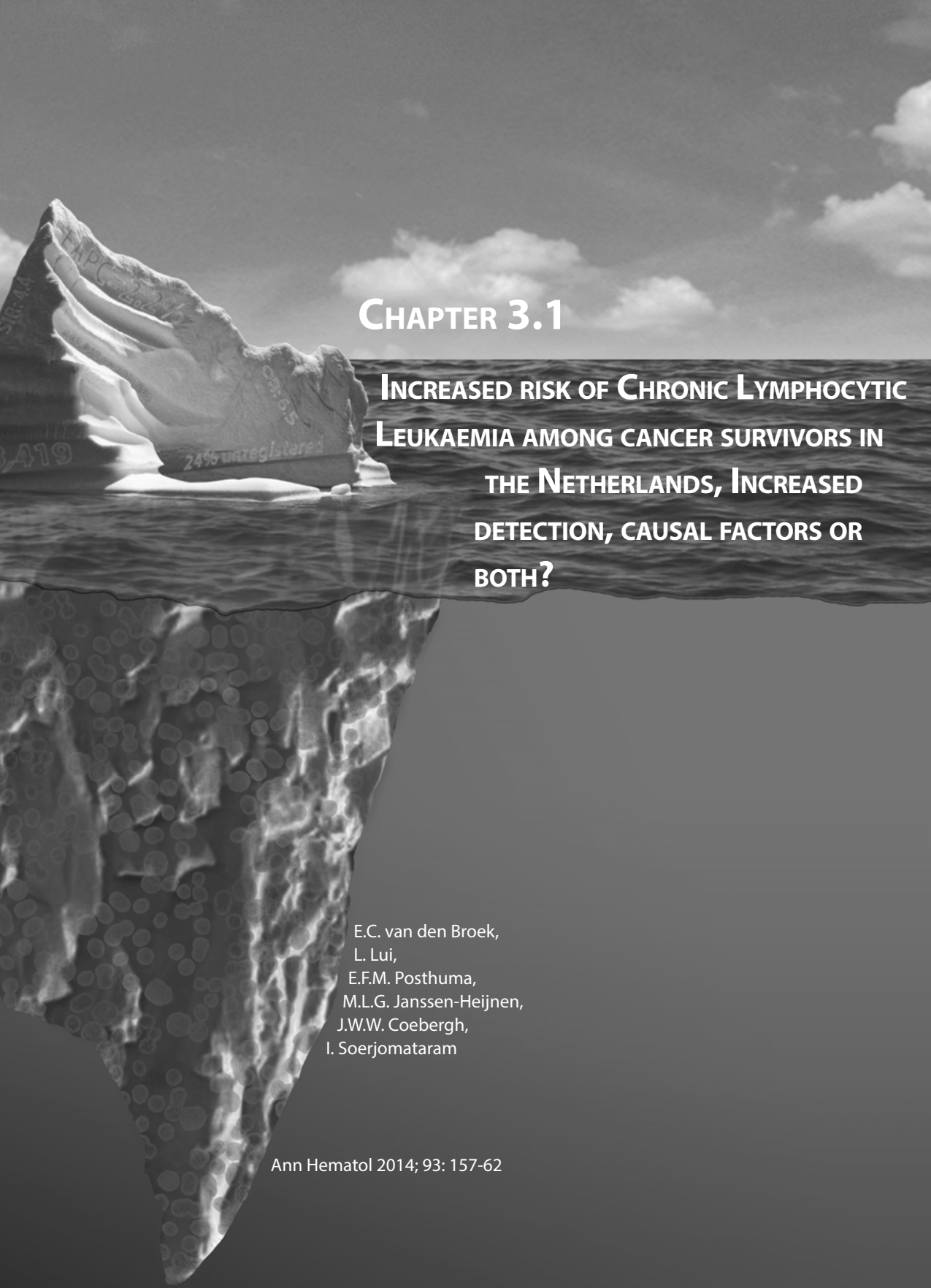


Chapter 3.

Chronic Lymphocytic Leukaemia in relation to other malignancies in the same patient



Chapter 3.1

Increased risk of Chronic Lymphocytic Leukaemia among cancer survivors in the Netherlands, Increased detection, causal factors or both?

E.C. van den Broek,
L. Lui,
E.F.M. Posthuma,
M.L.G. Janssen-Heijnen,
J.W.W. Coebergh,
I. Soerjomataram

Ann Hematol 2014; 93: 157-62

Abstract

We assessed the risk of Chronic Lymphocytic Leukaemia (CLL) following earlier primary malignancies (EPM) to explore the extent and determinants of this risk.

We used the Netherlands Cancer Registry data of 1,313,232 cancer survivors who were at risk to be subsequently diagnosed with CLL between 1989 and 2008. Cancer survivors were categorized based on gender, age, time since diagnosis of EPM and type of EPM. CLL was regarded synchronous when diagnosed within three months after diagnosis of EPM, metachronous CLLs were those diagnosed later.

Overall, we found that cancer survivors had a 90% higher risk to be diagnosed with CLL than the general population. In the first year after diagnosis we found a more than four-fold increased risk of CLL (Standardised Incidence Ratio (SIR): 4.4; 95%Confidence Interval (CI): 4.1-4.8), however no increased risk was observed after excluding synchronous cases. After one year, the excess risk of subsequent CLL ranged from 1.2 to 1.8. An increased risk for metachronous CLL was found in prostate (SIR: 1.3; 95%CI: 1.1-1.5) and squamous cell skin cancer survivors (SIR: 2.3; 95%CI: 1.9-2.7).

Intensive clinical check-ups after/around diagnosis of the EPM seemed to be the main cause for the increased risk of CLL among cancer survivors. Possible shared risk factors between prostate cancer or skin cancer and CLL can not be excluded. Further clinical research aimed at CLL as SPM is warranted since this comprises a complex group of patients with limited treatment options.

Introduction

Cancer survivors are often at increased risk for other malignancies, due to shared risk factors (e.g. genetic aberrations) or carcinogenicity of the treatment for the earlier malignancy (e.g. radiotherapy or alkylating agents).[1] As survival rates for most malignancies are rising,[2] the number of patients with more than one malignancy will increase too. Albeit studying determinants of the incidence of CLL as a Subsequent Primary Malignancy (SPM) could lead to better insights into the role of the aforementioned causal factors, literature on this topic is scarce.

An increased incidence of CLL among skin cancer survivors has previously been described. The authors suggested that shared aetiological factors such as genetic susceptibility, ultraviolet radiation and associated immune-suppression probably caused this increase.[3, 4]

Apart from causal factors, increased detection rates among cancer survivors could also result in higher incidence rates of subsequent malignancies. Cancer patients undergo many extensive check-ups that may increase the chance of CLL being detected coincidentally. An increase in incidence rates of CLL in the Netherlands among relatively young patients has been described, which is likely to be caused by increased detection rates among cancer survivors.[5]

Recently, it was demonstrated that overall survival and cancer-specific survival was decreased for several common cancers in patients with pre-existing CLL.[6] Alongside, treatment options for multiple malignancies are often limited. Because of the possible impact on prognosis and choice of therapy, it is important to determine the magnitude of the increased risk of CLL among cancer survivors and identify its determinants, so that an adequate follow-up strategy and tailored care can be offered to these patients.

Rather than studying all types of subsequent malignancies following a specific type of cancer, this paper describes the occurrence of a certain cancer, CLL, as a subsequent malignancy following the diagnosis of any earlier malignancy.

Patients and Methods

We retrieved all cancer cases diagnosed in the Netherlands between 1989 and 2008 from the Netherlands Cancer Registry (NCR) database which was fed by eight regional comprehensive cancer centres. We included all patients diagnosed with a malignancy (N=1,313,232) and followed these patients until death or end of follow-up (December 31, 2008), whichever came first. The history of malignancies was retrieved from the medical records and used to determine the order of the cancer diagnosis, according to the International Rules for Multiple Primary Cancers.[7]

CLL was defined as ICD-O-2 codes 9592 and 9803 and ICD-O-2 / ICD-O-3 codes 9670, 9800, 9820, and 9823 (in accordance to ICD-O-3, Small Lymphocytic Lymphoma was also regarded as CLL).[8] As CLL is easily detected in routine blood tests that are frequently performed immediately after cancer diagnosis, patients diagnosed within three months after diagnosis

of EPM were regarded as synchronous. The group of patients with a diagnostic interval of more than three months was indicated as metachronous.

Excess risk (standardised incidence ratio; SIR) was calculated as the ratio of the observed cases to the expected cases. The number of expected cases in the cohort was calculated based on the age-, gender- and calendar year-specific incidence rates for CLL in the general Dutch population, multiplied by the person-years at risk. 95% Confidence Intervals (95%CI) for SIR were calculated based on a Poisson distribution.[9]

SIRs were calculated according to gender and age at diagnosis of CLL, diagnosis interval and CLL (0-12 months, 13-60 months, 61-120 months and ≥120 months) and six sites of EPM (those that precede CLL in at least a 100 cases). In case of multiple EPM, age at diagnosis and diagnosis interval were based on the first primary malignancy (FPM). As different trends in CLL incidence rates were observed among persons aged 0-64 years, 65-74 years and ≥75 years and these differences might be associated with differences in the incidence of CLL as a SPM,[5] we chose to categorize age at diagnosis into these three categories. To assess the role of increased detection, all SIRs were calculated before and after exclusion of the synchronous cases.

SAS software (SAS system 9.2, SAS Institute, Cary, NC) was used to perform the statistical analyses.

Results

In the past 20 years, 1263 patients (816 males (65%) and 447 females (35%)) were recorded in the NCR with a diagnosis of CLL following a prior malignancy. This was 9.4 per cent of all CLL patients (in total, 13,419 CLL diagnoses were recorded in the NCR in those twenty years[5]). One-third of the subsequent CLL cases (430 patients) were regarded synchronous, as they were diagnosed within three months after the EPM was diagnosed. Almost half (48%) of the patients were older than 75 years at the time of the CLL diagnosis. Nine per cent of the patients with subsequent CLL had two or more prior malignancies (Table 1).

Table 1: *Characteristics of cancer survivors who developed a subsequent Chronic Lymphocytic Leukaemia (CLL) in the Netherlands in 1989-2008*

	Male	Female
Nr of patients	816	447
Age at diagnosis FPM		
0-64 years	224 (27%)	139 (31%)
65-74 years	318 (39%)	158 (35%)
75 years or older	274 (34%)	150 (34%)
Age at diagnosis of CLL as SPM		
30-64 years	138 (17%)	95 (21%)
65-74 years	288 (35%)	138 (31%)
75 years or older	390 (48%)	214 (48%)
Number of EPMs per patient		
1	734 (90%)	414 (93%)
2	70 (9%)	29 (6%)
3	9 (1%)	3 (1%)
> 3	3 (< 1%)	1 (<1%)

FPM: First Primary Malignancy, SPM: Subsequent Primary Malignancy, EPM: Earlier Primary Malignancy

Overall, cancer survivors had a 90% higher risk to be diagnosed with CLL than the general population (SIR 1.9; 95%CI: 1.8-2.0, Table 4). Table 2 shows that the increased risk of CLL was observed among all cancer survivors, regardless of gender and age. The excess risk ranged between 80% and 150%. After exclusion of synchronous CLL, increased risk was no longer observed in women younger than 75 years.

Table 2: *Standardized Incidence Ratio (SIR) according to age at diagnosis of subsequent Chronic Lymphocytic Leukaemia (CLL) for all cases and for metachronous cases only*

Age (years)	Synchronous and metachronous CLL cases						Metachronous CLL cases only					
	Males			Females			Males			Females		
	Obs	SIR	95%CI	Obs	SIR	95%CI	Obs	SIR	95%CI	Obs	SIR	95%CI
All	816	2.0*	1.9-2.1	447	1.8*	1.7-2.0	541	1.3*	1.2-1.4	292	1.2*	1.1-1.3
0-64	140	2.5*	2.1-2.9	95	1.9*	1.6-2.3	75	1.3*	1.1-1.7	60	1.2	0.9-1.6
65-74	287	1.9*	1.7-2.1	141	1.9*	1.6-2.2	193	1.3*	1.1-1.4	86	1.2	0.9-1.4
75+	389	2.0*	1.8-2.2	211	1.8*	1.5 -2.0	273	1.4*	1.2-1.5	146	1.2*	1.0-1.4

**) p< 0.05*
Obs: Observed cases, 95%CI: 95% Confidence Interval

The risk for subsequent CLL was elevated throughout the entire follow-up time after diagnosis of FPM. It was highest in the first year after FPM diagnosis (SIR: 4.4; 95%CI: 4.1-4.8), but only if synchronous cases were included (Table 3).

The six leading cancer sites to precede CLL were: prostate, breast, skin (squamous cell), colon/rectum, lung and haematological malignancies. The percentage of CLL diagnosed within three months after breast, lung and haematological cancers was equal to or higher than the overall percentage of synchronous CLL (34%), ranging from 34% for colon/rectum to 64%

for lung cancer. After exclusion of synchronous CLL, a significantly increased SIR was only found for prostate (SIR: 1.3; 95%CI: 1.1-1.5) and squamous cell skin cancer (SIR: 2.3; 95%CI: 1.9-2.7) (Table 4).

Table 3: *Standardized Incidence Ratio (SIR) for subsequent Chronic Lymphocytic Leukaemia (CLL) according to number of months since diagnosis of First Primary Malignancy (FPM)*

Months after diagnosis FPM	All			Males			Females		
	Obs	SIR	95%CI	Obs	SIR	95%CI	Obs	SIR	95%CI
0-12[a]	560	4.4*	4.1-4.8	368	4.3*	3.8-4.7	192	4.7*	4.1-5.5
4-12[b]	130	1.1	0.9-1.2	93	1.1	0.9-1.4	37	0.9	0.7-1.3
13-60	336	1.2*	1.1-1.3	225	1.2*	1.1-1.4	111	1.1	0.9-1.3
61-120	237	1.4*	1.3-1.6	150	1.5*	1.3-1.8	87	1.3*	1.0-1.6
>120	130	1.8*	1.5-2.1	73	1.9*	1.5-2.4	57	1.6*	1.2-2.1

a) Synchronous cases included
b) Synchronous cases excluded
**) p< 0.05*
Obs: Observed cases, 95% CI: 95% Confidence Interval

Discussion

We found 1263 patients with CLL following a prior malignancy over the past 20 years, which forms almost ten per cent of all newly diagnosed CLL cases. Overall, cancer survivors in the Netherlands had a 90% higher risk to be diagnosed with CLL than the general population.

A third of all subsequent CLL cases was diagnosed within three months after diagnosis of a FPM, whereas the median interval between a FPM and a general second malignancy (all types of second cancer) is three years.[10] The relatively short time to detection is a strong indication of increased detection in cancer survivors. CLL is often typically diagnosed coincidentally, when lymphocytosis is noticed during routine blood tests. At the time of or just after cancer diagnosis, intensive clinical check-ups might thus incidentally detect subclinical CLL that otherwise would remain undetected for a long time if not for ever.

Male cancer survivors who were younger than 65 years had the highest risk, if synchronous cases were included. The increased risk of metachronous CLL only was similar between males in all age categories. This is another indication for the role of increased detection. In the general population, men under the age of 65 have the lowest average number of doctor's consultations.[11] Hence, the difference in number of clinical check-ups (and therewith the chances of CLL being detected coincidentally) between cancer survivors and the general population is largest in this group.

The risk of subsequent CLL was elevated throughout the entire follow-up period. However, upon exclusion of synchronous cases, no excess risk was found in the first year after diagnosis of FPM. This was probably due to the high number of synchronous cases: Detecting many patients at a certain period at a subclinical phase, will cause a temporary increase in

Table 4: *Characteristics and Standardized Incidence Ratios (SIRs) of Earlier Primary Malignancies in patients who developed a subsequent Chronic Lymphocytic Leukaemia (CLL) in the Netherlands in 1989-2008*

	Prostate	Breast	Squamous cell skin	Colon/ rectum	Lung	Haematological	All
Nr of cases	**234**	**179**	**176**	**125**	**113**	**103**	**1263**
Follow-up time[#]							
< 12 months	21 (9%)	12 (7%)	16 (9%)	16 (13%)	60 (53%)	19 (18%)	208 (16%)
12-60 years	62 (27%)	49 (27%)	68 (39%)	33 (26%)	31 (28%)	43 (42%)	360 (29%)
60-120 months	94 (40%)	59 (33%)	58 (33%)	33 (26%)	12 (11%)	19 (18%)	364 (29%)
≥ 120 months	57 (24%)	59 (33%)	34 (19%)	43 (34%)	10 (9%)	22 (21%)	331 (26%)
Diagnosis interval							
< 3 months	51 (22%)	68 (38%)	35 (20%)	43 (34%)	72 (64%)	60 (58%)	430 (34%)
3-12 months	28 (12%)	5 (3%)	36 (20%)	11 (9%)	11 (10%)	6 (6%)	129 (10%)
12-60 months	89 (38%)	44 (25%)	60 (34%)	24 (19%)	16 (14%)	13 (13 %)	337 (27%)
60-120 months	51 (22%)	35 (20%)	34 (19%)	30 (24%)	11 (10%)	14 (14%)	237 (19%)
≥ 120 months	15 (6%)	27 (15%)	11 (6%)	17 (14%)	3 (3%)	10 (10 %)	130 (10%)
SIR (95%CI)							
Syn- and metachronous CLL[$]	1.6* (1.4-1.9)	1.7* (1.4-1.9)	2.9* (2.5-3.3)	1.7* (1.4-2.0)	2.5* (2.1-3.0)	3.0* (2.4-3.6)	1.9* (1.8-2.0)
Metachronous CLL only[$]	1.3* (1.1-1.5)	1.0 (0.8-1.2)	2.3* (1.9-2.7)	1.1 (0.9-1.4)	0.9 (0.7-1.2)	1.2 (0.9-1.7)	1.3* (1.2-1.4)

[#]) Follow-up time is time between diagnosis of EPM and death or end of follow-up
[$]) CLL was regarded synchronous when the diagnosis interval was <3 months and metachronous when it was ≥3 months.
**) p< 0.05*
95%CI= 95%Confidence Interval

incidence, followed by a decline, as all the cases that normally would be detected by the time the patient presented with symptoms are already diagnosed.

In general, CLL is not regarded as a radiation-induced cancer, and two earlier studies among patients with endometrium and prostate cancer showed that radiotherapy for these malignancies did not increase the risk of CLL.[12, 13] However, controversies on this issue persist.[14, 15] The relation between chemotherapy and subsequent development of CLL has been less intensively studied. Most studies of leukaemia after chemotherapy for a previous malignancy have excluded CLL.[16, 17] Our results corroborated the findings of previous studies that therapy for a prior cancer does not increase the risk of CLL as the risk is independent of time since diagnosis. No clustering of the risk around the expected lag time was observed. The lag time between radiation exposure and solid cancer development is at least a five year,[18] for haematological malignancies it is shorter.[19]

Not surprisingly, the most frequent sites of FPM to precede CLL were the sites with the highest incidence in the general Dutch population.[20] However, in general lung cancer contribute little to the incidence of SPMs, despite of its high incidence, because of its poor prognosis,[10] which is reflected in the short follow-up time. As intensified check-ups start soon after the diagnosis, they neutralise the effect of survival time on the incidence of SPMs, hence the emergence of lung cancer patient as one of the most common EPMs before CLL diagnosis.

For survivors of breast, colon/rectum, lung and haematological malignancies, the increased incidence of CLL seemed to be caused by increased detection as no significant increased risk was seen after exclusion of synchronous cases. For lung cancer and haematological malignancies the conjecture was strongest, as respectively 64% and 58% of the subsequent CLL cases were diagnosed within three months.

For prostate and squamous cell skin cancer the risk remained increased in the analyses of metachronous CLL only. Previous studies have already demonstrated a relationship between skin cancer and CLL, possible due shared aetiological factors (genetic susceptibility, ultraviolet radiation and associated immune-suppression).[3] Remarkably, the incidence of prostate cancer is decreased in skin cancer survivors, suggesting a protective effect of UVR on prostate cancer.[21] The occurrence of both CLL and prostate cancer in the same patient is less well documented. As the aetiology of both CLL and prostate cancer is largely unknown,[22] research into common risk factors could yield important insights. Although we corrected for differences in survival time of the preceding cancers, possible correlations between cancers with low survival rates and CLL could remain unnoticed as those patients do not survive long enough to actually develop a subsequent CLL. When the survival rates of these cancers increase, correlations with CLL might be found in the future, while it is not possible to reveal them now.

To our knowledge, this is the first study that uses high quality population-based national cancer registry data which guarantees the ample sample size and follow-up time, and representativeness of the results. However, this study is limited by the lack of data on risk factors, stage of CLL and details of prior treatment. Furthermore, we should bear in mind

that due to the long indolent course of the disease there is a possible delay in detection, causing CLL cases appearing to be the subsequent malignancy while they actually were the earlier one. This would lead to an overestimation of the SIRs. Alongside, the lack of pathology reports to signal new CLL cases results in an incomplete or delayed registration and hence an underreporting of the absolute number of (second) CLL cases. Since both the observed and the expected number of cases are affected by this phenomenon, we expect little influence on the SIRs.

In conclusion, increased detection seems to be the main determinant of the increased incidence of CLL among cancer survivors, but our results certainly do not rule out causal relations between CLL and EPM. Other risk factors such as common genetic susceptibility[23, 24] and viral infections,[25] known and not yet discovered by the current research community, may explain the higher incidence of CLL among cancer survivors. Possible shared risk factors for CLL and prostate or skin cancer merit attention as they could provide better insight in the aetiology of these malignancies.

As the number of cancer survivors is increasing, a significant increase of the number of patients with subsequent CLL will follow. They form a complex group of patients with limited treatment options and further clinical research aimed at this group is warranted, since they are excluded from almost all clinical trials.

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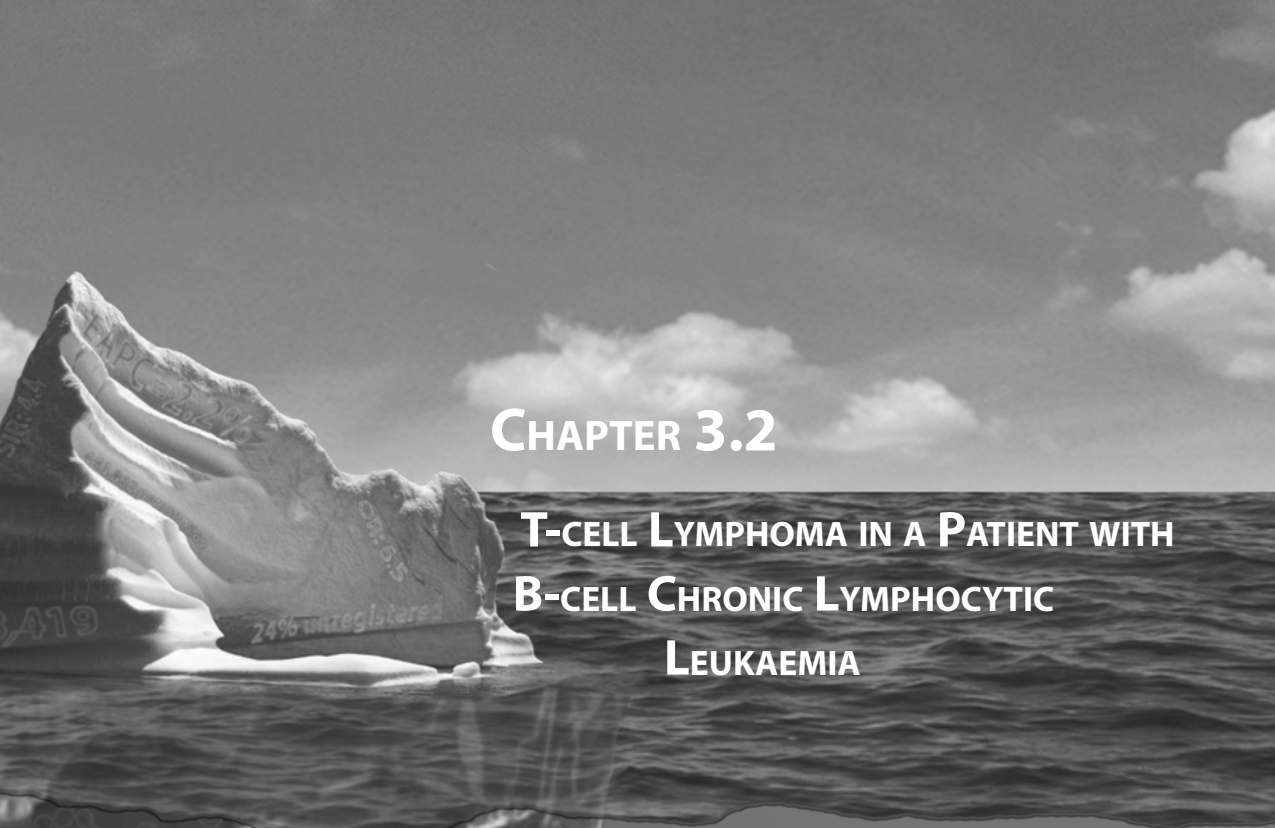

Chapter 3.2

T-cell Lymphoma in a Patient with B-cell Chronic Lymphocytic Leukaemia

G. Choi,*
E.C. van den Broek,*
O.C.G. Stam,
C.J.M. van Noesel,
S.H. Tonino,
A.P. Kater
* authors contributed equally to this manuscript

Submitted for publication

Abstract

We present a patient with chemotherapy-refractory chronic lymphatic leukaemia (CLL) in whom post-mortem examination showed hepatosplenomegaly, with both multiple small-cellular CLL lesions and large-cellular, monoclonal T-cell infiltrates. Following this case, the co-incidence of T-cell malignancies and CLL was studied using Dutch and American cancer registry databases. Analysis showed an excess risk for T-cell malignancies in CLL patients, with increased standardised incidence ratios compared with the general population and all cancer survivors in the databases. We hypothesize that CLL cells interact with T-cells in the microenvironment, facilitating malignant transformation.

Introduction

Chronic lymphocytic leukaemia (CLL) is a chronic lymphoproliferative disorder characterized by progressive accumulation of mature B-cells in peripheral blood and secondary lymphoid organs. Primary causes of death include infections and secondary malignancies[1], suggesting an immunodeficiency in CLL patients.[2] Recent epidemiological data demonstrated that the increased risk of other primary malignancies in CLL patients is independent of treatment or surveillance bias.[3] Most likely, CLL is not a disease limited to B-cells only, but also affects other components of the immune system due to extensive crosstalk between CLL cells and their microenvironment (reviewed by Burger[4]).

In this report, we present a patient with therapy-refractory CLL in whom eventually post-mortem examination revealed the presence of a T-cell lymphoma. We further studied the coincidence of T-cell malignancies and CLL within two population-based cancer registries, and found an excess risk of T-cell malignancies in patients with CLL.

Case report

A 75-year-old male patient with therapy-refractory CLL was referred to our hospital. CLL had been diagnosed 7 years earlier and was initially not treated (Rai 0). During the last 3 years, he was intermittently treated with Chlorambucil because of lymphadenopathy and/or leucocyte counts exceeding 100 x 10^9/l. One month before admission, he had a painful cervical node, from which a biopsy revealed CD5 positive, cycline-D1 negative B-cells, compatible with CLL and without signs of transformation. Local palliative radiotherapy was complicated by an abscess that was empirically treated with fluconazole and amoxicillin-clavulanic acid.

Upon admission, patient presented with fever, dysphagia, and general malaise. His blood counts showed a pancytopenia with haemoglobin 4.9 mmol/l (7.5 a month before), leucocytes 2.3 x 10^9/l (50% lymphocytes), and platelets 10 x 10^9/l (80 before). Without clinical signs of a specific infection, he was treated with broad-spectrum antibiotics. To exclude progressive disease, a bone marrow biopsy was performed, showing CLL cells with dysplastic pro-erythrocytes and a few haemophagocytes. Within hours, he had progressive respiratory failure due to either sepsis or transfusion-related lung injury. Despite ventilatory support, patient's condition rapidly deteriorated and he died within a few hours.

Post-mortem examination showed signs of multi-organ failure, including congested lungs without microbial infiltrates. There was hepato-splenomegaly and lymphadenopathy. Immunohistochemistry showed diffuse infiltrates of small, basophilic cells, positive for CD5, CD20 en CD23 (in liver, spleen, and bone marrow). Remarkably, the spleen contained, apart from CLL, areas with large cells with atypical nuclei positive for CD3 and CD8, and negative for CD4, CD5, CD20, CD23, CD79a, PAX-5, and keratin. Ki67 showed a high proliferation index in these areas. Altogether, this patient was found to have CLL and a high-grade T-cell lymphoma (see Figure 1). Molecular analyses of both spleen and liver lesions demonstrated clonal B-cell receptor and clonal T-cell receptor rearrangements, confirming these malignancies.

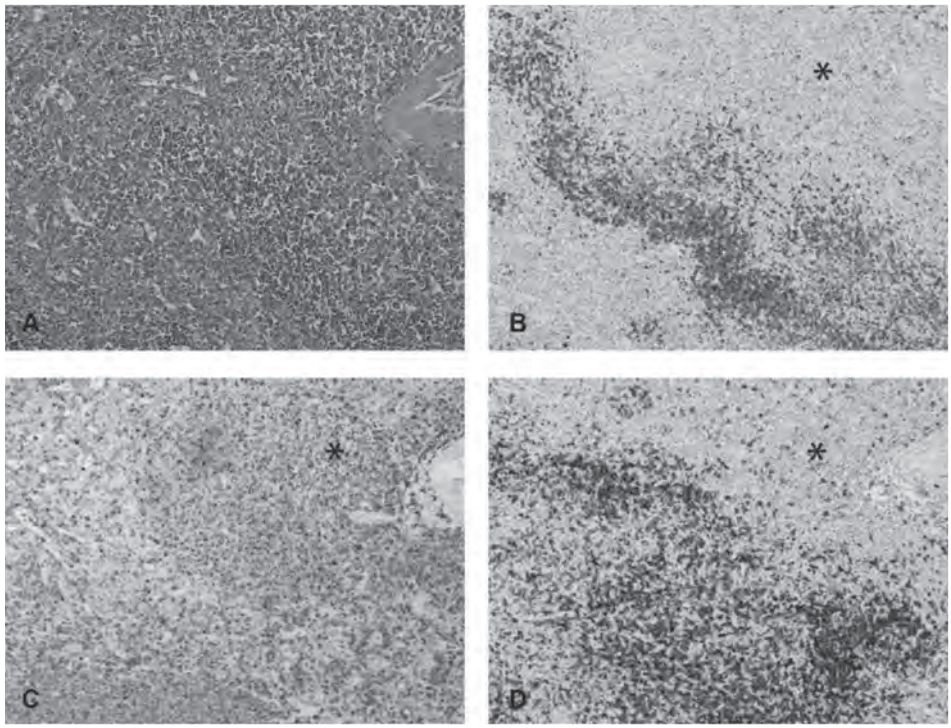

Figure 1: *Spleen section with T-cell lymphoma (*) and CLL, stained with (A) H&E, (B) CD79a, (C) CD3, (D) CD5 monoclonal antibodies (50x magnification).*

This case demonstrated that a large-cell T-cell lymphoma had developed in a patient with a chronic B-cell leukaemia. In the classical Richter's syndrome, CLL cells are believed to transform into a large cell B-cell lymphoma, after acquisition of additional molecular lesions.[5] Rarely, in large cellular lymphomas complicating CLL, there is no clonal relationship with CLL. There have been case reports of Hodgkin's disease[6-8] and T-cell lymphoma[9-11] found in CLL patients.

Cohort study

To estimate the incidence of T-cell lymphomas among CLL patients, we performed a retrospective study within the Netherlands Cancer Registry (NCR) database. We retrieved all cancer cases diagnosed in the Netherlands between 1989 and 2008 and included patients diagnosed with a first primary invasive cancer (N=1,270,595). Patients were followed until the occurrence of T-cell lymphoma, death, or end of follow-up (December 31, 2008). The order of the cancer diagnosis was determined according to the International Rules for Multiple Primary Cancers.[12] T-cell malignancies were defined as ICD-O-2 codes 9700-9702, 9705, 9708, 9714, 9716-9719, 9827, 9831, 9834, 9948 and ICD-O-3 codes 9591, 9593, 9675, 9680, 9684, 9702-9704, 9713, 9823, 9825 combined with type=T-cell. As a measure of excess risk, standardised incidence ratio (SIR) was calculated as the ratio of the observed number of cases in the cohort to the expected number of cases. The number of expected cases was

calculated by multiplying the person-years at risk by the age-, gender-, and calendar year-specific incidence rates in the background population. 95% Confidence Intervals (95% CI) for SIRs were calculated based on a Poisson distribution. SAS software (SAS system 9.3, SAS Institute, Cary, NC) was used to perform the statistical analyses.

As shown in Table 1, Dutch CLL patients exhibited a threefold excess risk of developing a T-cell malignancy when compared with the entire Dutch population (SIR 3.0; 95% CI: 1.3-5.8). To correct for possible increased detection among cancer survivors, we also compared CLL patients with all Dutch cancer survivors. This yielded a SIR of 1.7, however statistically non-significant (95% CI: 0.71-3.3). As this might be due to the small size of the cohort, we performed the same analysis on the Surveillance, Epidemiology and End Results (SEER) database. We retrieved all registered cancer cases diagnosed in the United States (US) of America between 1973 and 2010 and included patients diagnosed with a first primary invasive cancer (N=6,316,679). End of follow-up date was December 31, 2010. We found that US CLL patients exhibited a more than twofold risk for T-cell malignancies compared with all US cancer survivors (SIR 2.1; 95% CI: 1.7-2.7).

Table 1: *Increased rates of T-cell malignancy as a second primary malignancy in patients with CLL as compared with all cancer patients and the general population in the Netherlands (NCR) or United States of America (SEER).*

				Compared with			
	CLL patients			all cancers		general population	
	N	Time at risk (PY)	N (TCL)	SIR	95% CI	SIR	95% CI
NCR	13,504	61,631	8	1.7	(0.71-3.3)	3.0	(1.3-5.8)
SEER	90,721	443,802	72	2.1	(1.7-2.7)	n/a	

Discussion

We here presented a patient with therapy-refractory CLL who died from multi-organ failure, in whom a T-cell lymphoma was detected at post-mortem examination. Using analyses of the Dutch NCR database, we estimated that CLL patients had a threefold higher risk of T-cell lymphoma than the general population. To correct for detection bias, we calculated the risk among CLL-patients compared to cancer survivors, using the larger SEER database, and found a twofold excess risk. Considering the fact that diagnosis of T-cell lymphoma as a second primary malignancy can be challenging, we think that these presented SIRs will certainly not over-estimate the risk of malignant T-cell disease in CLL patients. In summary, epidemiological data corroborate the hypothesis that CLL predisposes patients for the development of T-cell malignancies. In CLL patients with an unexpected change in clinical condition, T-cell malignancies should be included in the differential diagnosis.

We propose that there is a biologic rationale for increased incidence of clonal T-cell disorders in CLL. In CLL, there is an expansion of T-cells with a globally impaired function characterized by a pseudo-exhausted phenotype.[13] Indeed, microarray and functional studies showed that T-cells from CLL patients undergo significant changes on a molecular and structural level.[14] Clearly, CLL cells and T-cells have reciprocal interactions, inducing both expansion and intrinsic changes. It remains to be investigated whether malignant transformation is facilitated through such interactions or other factors (e.g., previous treatment) play a role in the pathogenesis of T-cell malignancies in CLL patients.

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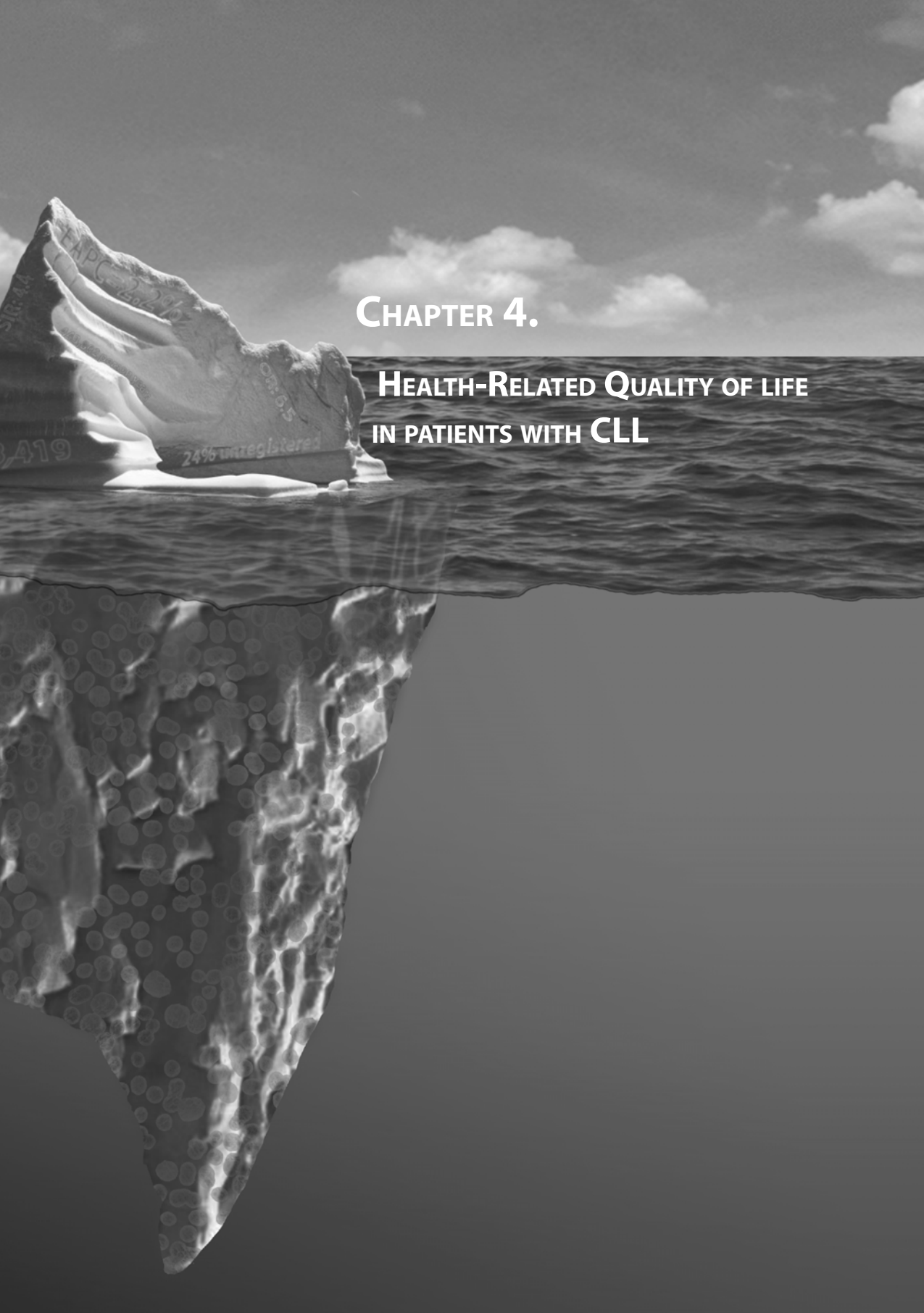
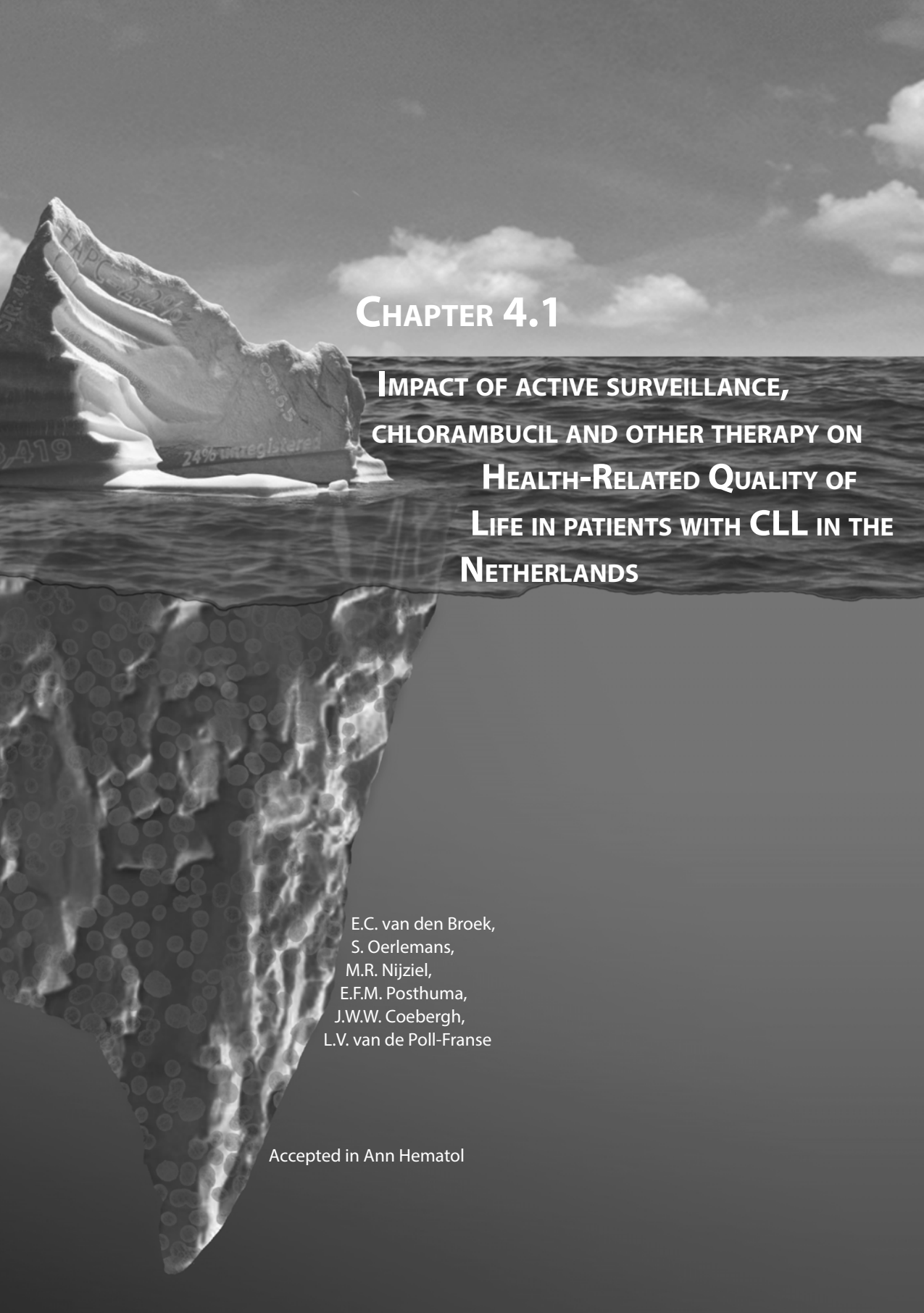


Chapter 4.

Health-Related Quality of life in patients with CLL



Chapter 4.1

Impact of active surveillance, chlorambucil and other therapy on Health-Related Quality of Life in patients with CLL in the Netherlands

E.C. van den Broek,
S. Oerlemans,
M.R. Nijziel,
E.F.M. Posthuma,
J.W.W. Coebergh,
L.V. van de Poll-Franse

Accepted in Ann Hematol

Abstract

As survival of patients with Chronic Lymphocytic Leukaemia/ Small Lymphocytic Lymphoma (CLL/SLL) increases and the number of patients who live long rises, health-related quality of life (HRQoL) becomes a relevant endpoint. Few studies investigated this, mainly as a secondary endpoint in randomized clinical trials where patients with early stage CLL/SLL, and elderly/frail patients were underrepresented. The aim of our study was to assess HRQoL in a population-based setting, including these previously underrepresented patients.

Out of 175 patients diagnosed with CLL/SLL between 2004 and 2011, 136 (78%) returned the HRQoL-questionnaire. The outcomes were compared to an age- and sex-matched norm population. Detailed data on stage and treatment were extracted from a population-based haematological registry (PHAROS).

Patients ever treated for CLL/SLL reported significantly poorer HRQoL than the norm population ($p<.01$ with large clinically important differences). Interestingly, no differences were observed between the norm population and patients under active surveillance. In contrast to our hypothesis, patients treated with chlorambucil reported the lowest HRQoL scores.

Drastic, long-lasting negative effects of starting treatment on HRQoL cannot be excluded, whereas active surveillance does not seem to provoke worrying, anxiety, or depressive symptoms. Further elaborate research into the impact of starting therapy on HRQoL is needed, especially in patients that are underrepresented in most clinical trials, and thoroughly consider its results during revision of treatment guidelines.

Introduction

Chronic Lymphocytic Leukaemia (CLL) is the most common type of leukaemia in adults in western countries, both in terms of incidence and prevalence. The incidence in Europe is 4.9 per 100,000 person years.[1]

Small Lymphocytic Lymphoma (SLL) is an indolent form of Non-Hodgkin Lymphoma with morphological and immunophenotypic features similar to CLL. Hence the most recent World Health Organization (WHO) classification scheme for haematopoietic malignancies considers CLL and SLL to be different manifestations of the same disease and combines these entities into one disease category; CLL/SLL.[2] Median survival time is 10 years, ranging from months when the disease behaves aggressively, to decades for patients with an indolent course of the disease.[3] Approximately 70% of the patients is older than 65 years at the time of diagnosis.[4]

Active surveillance remains standard practice for patients with asymptomatic, early stage CLL/SLL, as randomized clinical trials (RCTs) failed to show a statistically significant difference in survival between early versus deferred therapy.[5] For young and more or less fit patients with advanced disease, fludarabine, cyclophosphamide, and rituximab (FCR) became standard first line treatment, after a phase III study showed improvement of survival after addition of a monoclonal antibody in 2010.[6] During the study period, chlorambucil was the first choice for elderly and/or frail patients, as up until recently, no RCTs with this group of patients showed improved therapeutic results over chlorambucil.[7, 8] In 2014, the results of the CLL11-trial were published, which showed that combining an anti-CD20 antibody with chemotherapy improves outcomes in patients with CLL and coexisting conditions.[9]

Since the number of CLL/SLL patients who live long after their diagnosis is rising (due to improvement of response to treatment and survival rates), health related quality of life (HRQoL) is a relevant endpoint. Up to now, few studies have investigated HRQoL in CLL/SLL patients,[10-12] most as part of randomized clinical trials,[13] underrepresenting patients with early stage CLL/SLL, elderly patients and patients with comorbidities. The aim of the present study was therefore to assess HRQoL in a population-based setting that includes these previously underrepresented patients. We evaluated HRQoL among patients on and off treatment with different treatment modalities and subsequently compared this with an age-and sex-matched norm population to assess the effect of CLL. We hypothesize that patients who received chlorambucil report better HRQoL than patients receiving other chemo-/immunotherapy, as chlorambucil is associated with less toxicity then most other regimens.[14] We expect patients in the active surveillance group to report better HRQoL than patients that were treated, as they neither suffer from symptoms nor from side effects of active treatment. Furthermore, we expect that patients who were undergoing treatment during survey completion to report a worse HRQoL than patients who were off treatment, as they experience more effect of the disease on their daily life during treatment. Finally, we expected that active surveillance without treatment provokes feelings of uncertainty; leading to worrying, anxiety and depressive symptoms as this was observed in men with prostate cancer under active surveillance.[15]

Patients and methods

Setting and population

This study took place within the scope of the Population-based HAematological Registry for Observational Studies (PHAROS; www.pharosregistry.nl). PHAROS is a supplement to the Netherlands Cancer Registry (NCR), which is maintained and hosted by Comprehensive Cancer Centre South (CCCS) and Comprehensive Cancer Centre the Netherlands (CCCNL). The NCR was used to select all patients in an area covering approximately 40% of the Dutch population, who were diagnosed with CLL or SLL as defined by the International Classification of Diseases for Oncology-3 codes (ICD-O-3)[16] between January 1st, 2004 and January 1st, 2011. The NCR-data of these patients were replenished with details on stage, (response to) treatment and adverse events.

Additionally, a dynamic longitudinal population-based survey was set up among CLL/SLL patients registered with the Eindhoven Cancer Registry (ECR) of the CCCS, which is a component of NCR. Patients diagnosed between January 1st, 2004 and January 1st, 2011 were linked with the database of the Central Bureau for Genealogy, which collects data on all deceased Dutch citizens through the civil municipal registries, to exclude patients who had deceased. In this survey, patient reported outcomes were collected within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors. PROFILES contains a large web-based component and is linked directly to clinical data from ECR. Details of the data collection method are previously described.[17] Data from the PROFILES registry are available for non-commercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration (www.profilesregistry.nl).

Ethical approval for the study was obtained from a certified Medical Ethics Committee (of the Maxima Medical Centre in Veldhoven, The Netherlands; number 0734).

Study measures

General information was available from the NCR that routinely collects data on tumour characteristics, including date of diagnosis and morphology, and patient's background characteristics, including gender and date of birth. Detailed clinical information was available from the PHAROS-registry that collects additional data including stage and treatment.

We divided patients in treatment categories with hypothesized impact on HRQoL, from most to least: 1) 'R-CHOP', 'FC(R)', '(R-)CVP / Rituximab (+/- Chlorambucil) / Fludarabine monotherapy', (indicated as 'other chemo- and/or immunotherapy') 2) 'Chlorambucil', 3) 'Radiotherapy', 4) 'Active surveillance', and 5) 'No treatment' (e.g. patients who fulfil treatment criteria but refuse therapy).

Patients were considered off treatment if the most recent therapy was administered more than three months prior to the date of filling in the questionnaire. Otherwise, patients were considered on treatment.

The Dutch validated version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) was used to assess HRQoL.[18] Answer categories range from one (not at all) to four (very much). After linear transformation, all scales and single item measures range in score from 0 to 100. A higher score on function scales and global health and quality of life scale implies a better HRQoL, whereas for symptoms a higher score refers to more symptoms.[18]

Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS). In this questionnaire, anxiety and depressive symptoms are measured in two separate subscales of seven items each. Answers range from 0 to 3, and a score ≥8 on either subscale indicates a substantial level of anxiety or depressive symptoms.[19, 20]

Worry was assessed with the items "Worry about future", "Worry about health", "Worry about cancer coming back" and "Worry when new symptoms occur" of the Impact of Cancer Scale (IOC). This measure presents statements to which respondents indicate their level of agreement from 1 (strongly disagree) to 5 (strongly agree).[21, 22]

Co-morbidity at the time of survey was categorized according to the Self-Administered Comorbidity Questionnaire (SCQ). Survivors' marital status and educational level were also assessed in the questionnaire.

Data collection

Patients were included on three time points: May 2009 (patients diagnosed between January 1999 and May 2008); November 2009 (patients diagnosed between May 2008 and May 2009) and May 2011 (patients diagnosed between May 2009 and December 2010).

In order to compare outcomes with those from a normative population we also collected the EORTC QLQ-C30, SCQ[23], marital status and educational level data among 1352 persons without cancer.[24] From this normative population an age- and sex-matched selection was made of 209 persons to compare HRQoL with the CLL patients. For matching, ten strata were formed using sex and age (5 categories). Within each stratum, a maximum number of persons from the reference cohort were randomly matched according to the strata frequency distribution of the patients. This resulted in 209 matched cancer-free individuals for 136 patients.

Statistical analyses

All statistical analyses were performed using SAS (version 9.3 for Windows; SAS Institute Inc., Cary, NC). P values of <.05 were considered statistically significant. Clinically relevant differences were determined using the evidence-based guidelines for interpretation of the EORTC QLQ-C30 between groups.[25]

Patients were determined to be fatigued with an EORTC QLQ-C30 fatigue score >21.9 (mean normative population + small clinically important difference, i.e. 5 points) and low physical functioning was defined as an EORTC QLQ-C30 score <83.2 (mean normative population -

small clinically important difference, i.e. 5 points). Patients were considered having anxious symptoms with a HADS anxiety score >8 and having depressive symptoms with a HADS depression score >8.20 Worry about health and worry about future were considered positive if patients (strongly) agreed with this item.

Differences in demographic and clinical characteristics between respondents, non-respondents, and patients with unverifiable addresses and between treatment groups were compared with chi-square analyses and Fisher exact with Montecarlo estimate tests.

Differences in mean EORTC QLQ-C30 scores between CLL/SLL survivors under active surveillance and CLL/SLL survivors treated with chemo- and/or immunotherapy versus an age- and sex-matched Dutch normative population were compared with analysis of variance (ANOVA).

Analysis of covariance (ANCOVA) was carried out to investigate the differences in mean EORTC QLQ-C30, HADS and IOC Worry scores between treatment groups and between on and off treatment after adjustment for sex, age and comorbidity.

Logistic regression models using the dichotomized EORTC QLQ-C30 physical functioning and fatigue scores, HADS anxiety and depression scores and IOC Worry items as outcomes, were conducted to identify variables associated with these outcomes. These were the outcomes that were mentioned to be affected most often in both focus groups and previous studies.[26, 27] Variables were a priori determined, including gender, age, number of comorbidities, time since diagnosis and treatment.

Results

Patients' characteristics

We analysed data of 200 CLL/SLL patients of whom 175 received a questionnaire that was returned by 136 (78% response rate). Despite the population-based nature of the study, not all eligible patients received a questionnaire. One hundred eight patients did not receive a questionnaire as they were treated in hospitals that did not participate in the survey. We did not expect this to affect the representativeness. Another 37 patients did not receive a questionnaire because their specialist indicated they had other severe medical problems. This could have resulted in slightly better HRQoL-outcomes. (Figure 1).

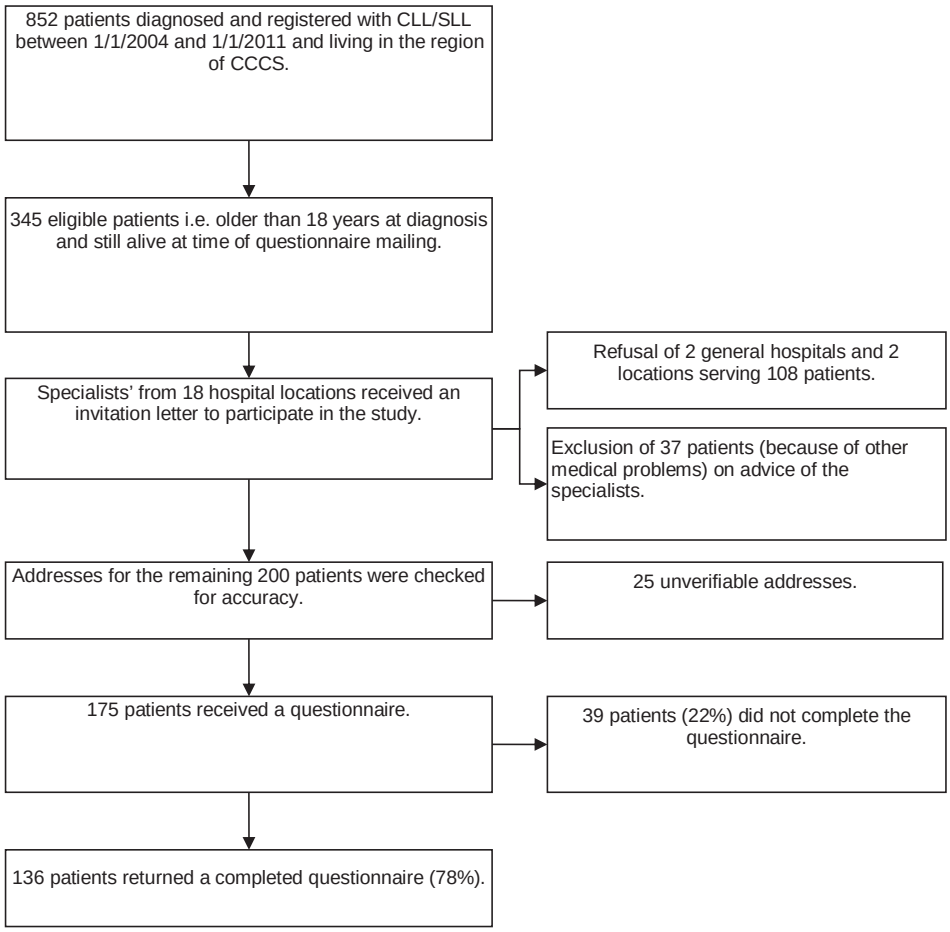


Figure 1: *Flow chart of the data collection process*

Non-respondents were significantly older than respondents and patients with unverifiable addresses (mean age at diagnosis 67.7 years versus 63.1 and 61.5 years, respectively). Non-respondents were more often under active surveillance and diagnosed with an early stage, however those differences were not statistically significant. Almost half of the respondents (47%) were diagnosed less than two years prior to survey completion, and active surveillance was the most frequent treatment strategy (49%). Thirty-nine percent of the responding patients were diagnosed with Rai-stage 0. Slightly more than half of the respondents (53%) were younger than 65 years. Seventy-one percent of the patients reported one or more comorbid conditions, the most common were high blood pressure (27%), anaemia (22%) and back pain (22%) (Table 1).

Table 1: *Sociodemographic and clinical characteristics of questionnaire respondents, non-respondents, and patients with unverifiable addresses.*

	Respondents (N=136)	Non-Respondents (N=39)	Patients with unverifiable addresses (N=25)	
	N (%)	N (%)	N (%)	P-value
Gender				0.60
Male	90 (67)	26 (67)	14 (56)	
Female	46 (33)	13 (33)	11 (44)	
Age: mean (SD)	63.1 (10.5)	67.7 (11.0)	61.5 (14.1)	<0.05
<55 years	31 (23)	6 (15)	7 (28)	
55-64 years	41 (30)	4 (10)	7 (28)	
65-74 years	46 (34)	17 (44)	7 (28)	
75+ years	18 (13)	12 (31)	4 (16)	
Treatment				0.19
R-CHOP	4 (3)	0 (0)	1 (4)	
FC(R) / Fludarabine	10 (7)	2 (5)	1 (4)	
(R-)CVP/ Rituximab	16 (12)	4 (10)	2 (8)	
Chlorambucil	27 (20)	1 (3)	7 (28)	
Radiotherapy	3 (2)	2 (5)	1 (4)	
Active surveillance	68 (51)	26 (67)	12 (48)	
None	8 (6)	4 (10)	1 (4)	
Years since diagnosis: mean (SD)	2.7 (1.3)	2.6 (1.4)	2.9 (1.4)	0.36
<2 year	65 (48)	16 (41)	9 (36)	
2-3 years	28 (21)	9 (23)	3 (12)	
≥ 3 years	43 (32)	14 (36)	13 (52)	
Stage at diagnosis				0.87
Rai 0	53 (39)	21 (54)	11 (44)	
Rai 1	25 (18)	6 (15)	6 (24)	
Rai 2	16 (12)	4 (10)	3 (12)	
Rai 3	4 (3)	0 (0)	0 (0)	
Rai 4	7 (5)	0 (0)	0 (0)	
Not Applicable (SLL)	31 (23)	8 (21)	5 (20)	
Number of self reported co-morbidities				
0	28 (21)			
1	31 (23)			
≥2	66 (48)			
Unknown	11 (8)			
Marital Status				
Partner	105 (77)			
Divorced	11 (8)			
Widowed	13 (9)			
Alone	4 (2)			
Education[$]				
High	28 (20)			
Middle	71 (51)			
Low	34 (25)			

Note: SLL= Small Lymphocytic Lymphoma;
[$]Education levels included low = no/primary school; medium = lower general secondary education/ vocational training; or high = pre-university education/ high vocational training/university.

As expected, patients under active surveillance had more often been diagnosed at an early stage than patients who had received chemo- and/or immunotherapy. Although the patients in the chlorambucil group were older than the patients in the other groups (55% being older than 65 years versus 46% in the active surveillance group and 44% in the other chemo-group), and patients under active surveillance were more often males (70% versus 63% and 57% in the chlorambucil-group and other chemo-group respectively), none of the differences other than stage were statistically significant. (Table 2).

Comparison CLL/SLL patients with age- and sex-matched normative population
CLL/SLL patients treated with chemo- and/or immunotherapy had statistically significantly worse scores on all HRQoL scales (all p <.001) except for pain, constipation and diarrhoea, compared to an age- and sex-matched normative population. A medium clinically important difference was observed for social functioning, fatigue, dyspnoea, sleeping problems and financial problems. Other scores represented small clinically important differences. Differences between CLL/SLL survivors under active surveillance and the normative population were not statistically or clinically significant (Figure 2).

Comparison between treatment groups
Compared to patients under active surveillance, patients having received any type of chemo- and/or immunotherapy reported worse scores on physical and role functioning and had more financial problems. Patients treated with chlorambucil also reported worse scores on social functioning and dyspnoea compared to patients under active surveillance. The prevalence of fatigue among the chlorambucil group (81%) was almost twice as high compared to the active surveillance group (42%) ($p<0.01$), and also higher than those treated with other chemo-/immunotherapy (63%), although not statistically significant. Similarly, patients treated with chlorambucil were also more worried about the future, their health, the cancer coming back and the occurrence of new symptoms than patients in the active surveillance group or patients treated with other chemo-/immunotherapy; although the latter did not reach statistical significance. No difference was observed for anxiety and depressive symptoms between any of the treatment groups (Table 3).

Table 2: *Socio-demographic and clinical characteristics of respondents according to treatment regime.*

	Patients under active surveillance N=68	Patients receiving Chlorambucil N=27	Patients receiving other chemo N=30	
	N (%)	N (%)	N (%)	P-value
Gender				0.4
Male	48 (70)	17 (63)	17 (57)	
Female	20 (30)	10 (37)	13 (43)	
Age: mean (SD)	64.9 (10.8)	68.8 (9.8)	64.2 (2.5)	0.6
<55 years	14 (21)	4 (15)	9 (30)	
55-64 years	23 (34)	8 (30)	8 (27)	
65-74 year	23 (34)	9 (33)	11 (37)	
75+ years	8 (12)	6 (22)	2 (7)	
Time since diagnosis: mean (SD)	2.3 (1.3)	2.9 (1.4)	2.5 (0.9)	0.1
<2 year	40 (59)	8 (30)	15 (50)	
2-3 years	12 (18)	7 (26)	8 (27)	
≥3 years	16 (24)	12 (44)	7 (23)	
Treatment phase				0.6
On treatment	NA	8 (30)	7 (23)	
Off treatment	NA	19 (70)	22 (73)	
Stage at diagnosis				<.0001
Rai 0	38 (56)	5 (19)	6 (20)	
Rai 1	17(25)	5 (19)	3 (10)	
Rai 2	5 (7)	7 (26)	4 (13)	
Rai 3	0 (0)	3 (11)	1 (3)	
Rai 4	0 (0)	3 (11)	3 (10)	
Not Applicable (SLL)	8 (12)	4 (15)	13 (43)	
Self reported comorbidities				0.9
No co-morbidities	15 (25)	4 (16)	8 (28)	
1 co-morbidity	18 (30)	9 (36)	9 (31)	
2 or more co-morbidities	28 (46)	12 (48)	13 (41)	
Marital Status				0.1
Partner	55 (82)	17 (65)	23 (77)	
Divorced	5 (7)	4 (15)	2 (7)	
Widowed	6 (9)	5 (19)	2 (7)	
Alone	1 (1)	0 (0)	3 (10)	
Education level[$]				0.7
High	14 (21)	6 (23)	4 (13)	
Medium	34 (52)	13 (50)	20 (67)	
Low	18 (27)	7 (27)	6 (20)	

Note: NA= Not Applicable; SLL= Small Lymphocytic Lymphoma;

[$]Education levels included low = no/primary school; medium = lower general secondary education/ vocational training; or high = pre-university education/ high vocational training/university.

Figure 2A and 2B: *Differences on EORTC QLQ-C30 mean functioning and global quality of life scores (Fig. 2A) and on EORTC QLQ-C30 mean symptom scores (Fig. 2B) of CLL/SLL patients treated with chemo and/or immunotherapy (N=57) and CLL/SLL patients under active surveillance (N=68) compared to an age- and sex-matched normative population (N=290).*

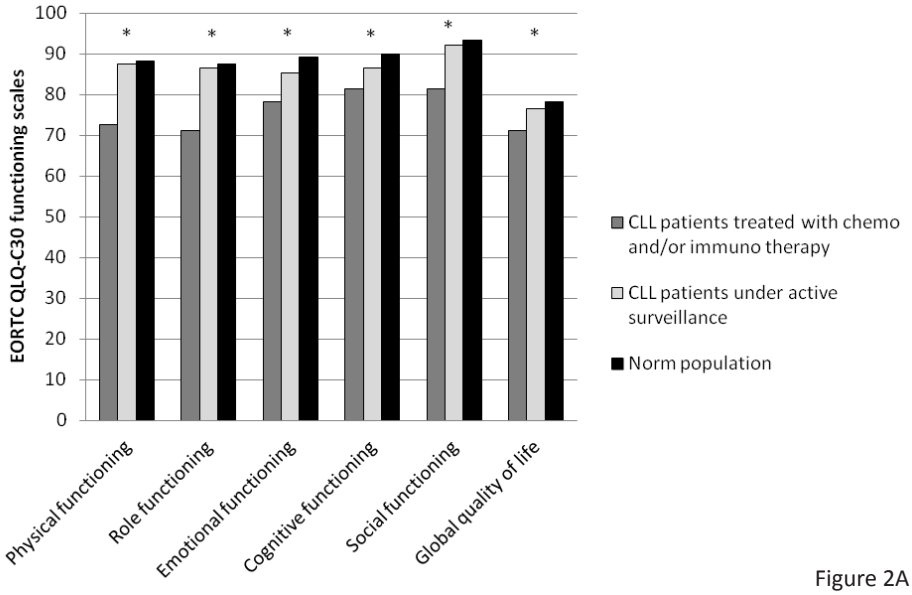


Figure 2A

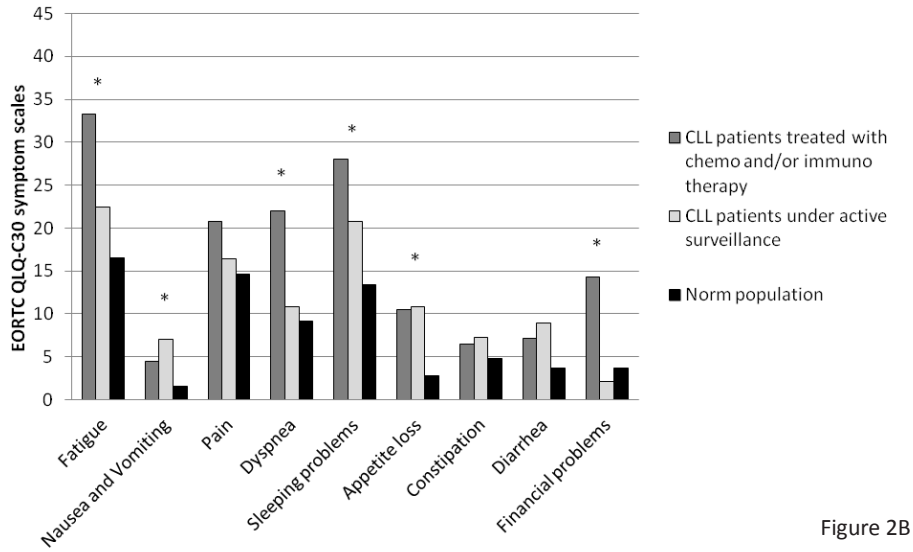


Figure 2B

EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core30; CLL= Chronic Lymphocytic Leukemia; SLL= Small Lymphocytic Leukemia.

For figure 2A goes: Higher scores imply a better health-related quality of life. For figure 2B goes: Higher scores imply more symptoms

**p<.01 and clinically important difference between CLL/SLL patients treated with chemo and/or immunotherapy compared to the normative population; Differences between CLL/SLL patients under active surveillance and the normative population were not statistically or clinically significant.*

Table 3: *Differences between CLL/SLL patients under active surveillance, CLL/SLL patients treated with Chlorambucil and CLL/SLL patients treated with other chemo and/or immunotherapy on EORTC QLQ-C30, HADS and IOC Worry.*

	Active surveillance N=68	Chlorambucil N=27	Other chemo-/ immunotherapy N=30	p-value*	Clinical importance
EORTC QLQ-C30	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**		
Physical Funct.	87.4 (18)	69.8 (22)	75.2 (20)	<.01[a,b]	a:medium, b:small
Role Funct.	86.5 (23)	72.8 (30)	69.4 (29)	<.01[a,b]	a, b: small
Emotional Funct.	85.2 (19)	71.2 (31)	84.6 (20)	<.05[a]	a: small
Cognitive Funct.	86.5 (20)	80.8 (32)	81.7 (21)	NS	
Social Functioning	92.2 (18)	79.5 (24)	82.8 (25)	<.01[a]	a: medium
Global health status/QoL	76.6 (20)	71.9 (17)	70.6 (19)	NS	
Fatigue	22.4 (27)	35.5 (24)	31.5 (29)	NS	
Nausea / Vomiting	7.0 (18)	4.5 (9)	4.4 (11)	NS	
Pain	16.4 (26)	24.4 (28)	17.8 (25)	NS	
Dyspnoea	10.8 (20)	23.1 (31)	21.1 (24)	<.05[a]	a: medium
Insomnia	20.8 (30)	30.8 (35)	25.6 (30)	NS	
Appetite loss	10.8 (26)	8.6 (18)	12.2 (22)	NS	
Constipation	7.3 (16)	6.4 (16)	6.7 (16)	NS	
Diarrhoea	8.9 (20)	9.0 (15)	5.6 (20)	NS	
Financial Problems	2.1 (8)	12.8 (27)	15.6 (27)	<.01[a,b]	a, b: medium
% Fatigue cases	43%	81%	63%	<.01[a]	
HADS					
Anxiety	4.5 (3.7)	6.0 (4.2)	3.5 (3.7)	NS	
Depression	3.6 (3.5)	4.9 (4.1)	4.1 (4.1)	NS	
% Anxiety cases	18%	33%	20%	NS	
% Depression cases	13%	30%	20%	NS	
IOC[+]					
Worry about future	16%	42%	24%	.02[a]	
Worry about health	27%	67%	31%	<.01[a]	
Worry about cancer coming back	28%	67%	48%	<.01[a]	
Worry when new symptoms occur	21%	46%	43%	.03[a]	

Note: CLL= Chronic Lymphocytic Leukaemia; SLL= Small Lymphocytic Lymphoma; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core30; HADS=Hospital Anxiety and Depression Scale; IOC=Impact of Cancer Scale.

**p-value is adjusted for age, sex, and number of co-morbidities;*

[a] Difference significant between the active surveillance group and the chlorambucil group;

[b] Difference significant between the active surveillance group and the other chemo/immunogroup.

[+] Percentage of patients who answered these IOC items with "agree" or "strongly agree".

Patients were defined as fatigue case with an EORTC QLQ-C30 fatigue score of >21.9 (mean norm population + small clinical important difference). Patients were defined as an anxiety case with a HADS anxiety score of >8. Patients were defined as a depression case with a HADS depression score >8.

Comparison patients on and off treatment
Compared to an age- and sex-matched normative population, CLL/SLL patients receiving treatment at survey completion scored worse on physical and social functioning, global quality of life, fatigue and sleeping problems with large clinically important differences. Medium clinically important differences were reported for role functioning and pain. For emotional and cognitive functioning the differences between CLL/SLL patients on treatment and the normative population were considered small clinically important.

CLL/SLL patients who no longer received treatment at survey completion scored worse on dyspnoea, sleeping problems and financial problems (medium clinically important differences). For physical-, role-, emotional-, and social functioning, fatigue and appetite loss the differences between CLL/SLL patients off treatment and the normative population were considered of small clinically importance.

A significantly and large clinically important difference on cognitive functioning was observed between patients still on treatment and patients off treatment ($p < 0.01$, Figure 3).

Socio-demographic, disease and treatment variables associated with HRQoL and worry
Multivariate logistic regression analysis showed that low EORTC physical functioning score was positively associated with co-morbidity and treatment. High fatigue scores and health worries were both positively associated with having two or more comorbidities and treatment with chlorambucil. Worrying about the future was negatively associated with age and positively associated with treatment with chlorambucil. No statistically significant associations were observed between HADS anxiety and depressive symptoms and sociodemographic, disease and treatment characteristics (Table 4).

Figure 3A and 3B. *Differences on EORTC QLQ-C30 mean functioning and global quality of life scores (Fig. 3A) and on EORTC QLQ-C30 mean symptom scores (Fig. 3B) of CLL/SLL patients on treatment (N=15) and CLL/SLL patients off treatment (N=42) compared to an age and sex-matched normative population (N=209).*

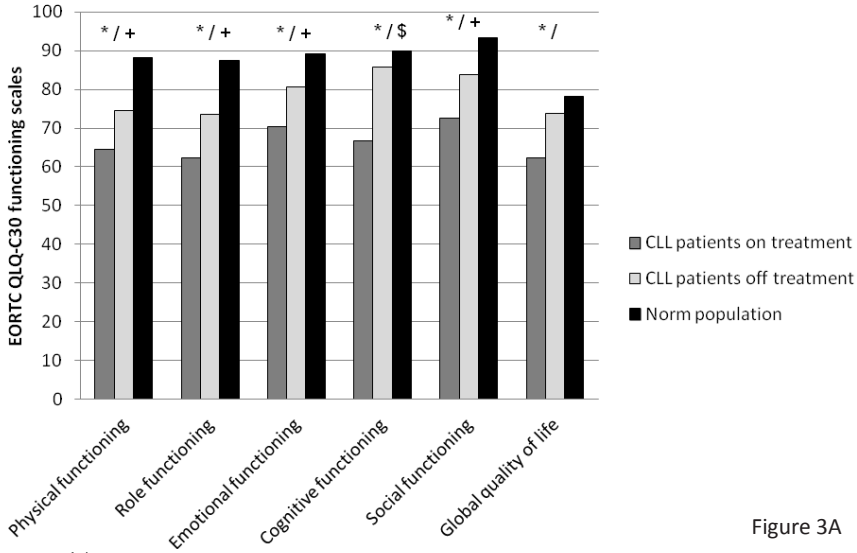


Figure 3A

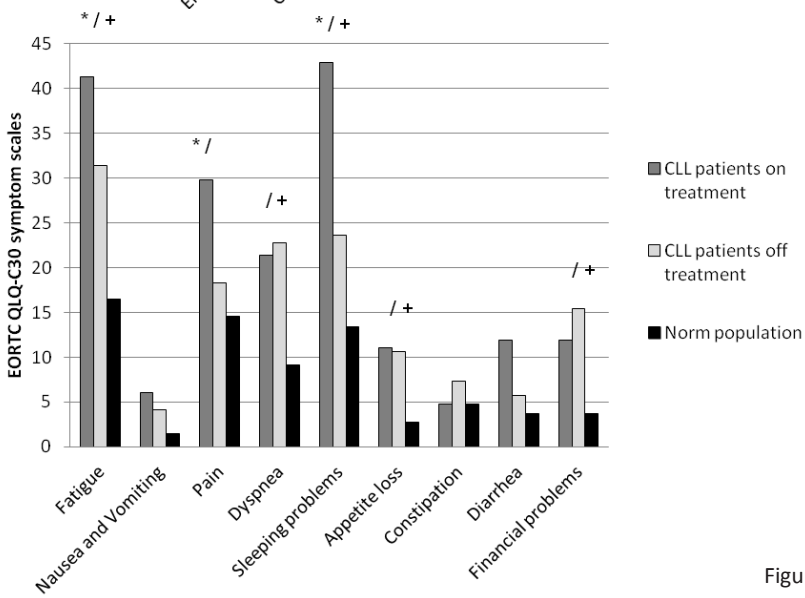


Figure 3B

EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core30; CLL= Chronic Lymphocytic Leukemia; SLL= Small Lymphocytic Leukemia.

*Figure 3A: Higher score imply better health-related quality of life. *=p<.05 and clinically important difference between CLL/SLL patients on treatment and the normative population. +=p<.05 and clinically important difference between CLL/SLL patients off treatment and the normative population. $=p<.05 and clinically important difference between CLL/SLL patients on and off treatment.*
*Figure 3B: Higher scores imply more symptoms. *=p<.01 and clinically important difference between CLL/SLL patients on treatment and the normative population. +=p<.01 and clinically important difference between CLL/SLL patients off treatment and the normative population.*

Table 4: *Odds ratios with confidence intervals (CI) of the multivariate logistic regression model evaluating independent variables for worse physical functioning, high fatigue, high worry about health and high worry about future scores for CLL/SLL patients (N=136).*

	Low Physical functioning (EORTC QLQ-C30) Odds ratio (95% CI)	High Fatigue (EORTC QLQ-C30) Odds ratio (95% CI)	High Worry about health (IOC) Odds ratio (95% CI)	High Worry about future (IOC) Odds ratio (95% CI)
Age	1.0 (0.99-1.1)	1.0 (0.96-1.0)	0.98 (0.94-1.0)	0.95 (0.90-0.99)*
Gender				
Male	Reference	Reference	Reference	Reference
Female	2.4 (0.92-6.4)	1.2 (0.53-2.9)	2.0 (0.78-5.1)	1.2 (0.42-3.4)
Comorbidity				
No co-morbidities	Reference	Reference	Reference	Reference
1 co-morbidity	5.1 (1.4-19.5)*	2.1 (0.73-6.0)	3.4 (0.97-11.7)	2.9 (0.71-11.7)
2 or more co-morbidities	16.8 (4.3-65.4)*	2.9 (1.1-7.6)*	4.0 (1.2-13.1)*	3.5 (0.88-13.5)
Treatment				
Active surveillance	Reference	Reference	Reference	Reference
Chlorambucil	10.5 (3.0-36.9)*	5.9 (1.7-20.0)*	6.5 (2.0-20.7)*	4.8 (1.4-16.6)*
Other chemo	9.9 (2.9-34.3)*	2.0 (0.78-5.0)	0.98 (0.34-2.9)	1.5 (0.45-5.1)
Time since diagnosis	0.89 (0.63-1.3)	1.1 (0.76-1.5)	0.76 (0.50-1.2)	0.80 (0.50-1.3)

*Note. *p<.05; No statistically significant associations were observed between HADS anxiety and depression and these characteristics.*
Low physical functioning was defined as an EORTC QLQ-C30 physical functioning score < 83.2 (mean norm population-small clinically important difference) (N=52). High fatigue was defined as an EORTC QLQ-C30 fatigue score > 21.9 (mean norm population + small clinically important difference) (N=70). High worry about health was defined as answered that item with agree or strongly agree (N=39). High worry about future was defined as answered that item with agree or strongly agree (N=25).

Discussion

In contrast to our hypothesis, patients treated with chlorambucil reported poorest HRQoL. Being treated for CLL/SLL was associated with deteriorated HRQoL longer after treatment than we anticipated, as both patients on and off treatment scored worse on fatigue, sleeping problems and all functional scales (except cognitive functioning) compared to the norm population. We expected patients in the active surveillance group to worry most, but patients treated with chlorambucil worried significantly more. No significant differences in reported anxiety or depressive symptoms between the treatment groups were found.

Although the combination of the observed significantly worse HRQoL for CLL/SLL patients treated with chemo- and/or immunotherapy compared to the active surveillance group, and the lack of differences between CLL/SLL survivors under active surveillance and the normative population, suggests that treatment is responsible for the poorer HRQoL and not so much the disease itself, it is also possible that disease severity (stage) could explain the observed association between treatment and HRQoL, as treatment is generally not initiated until the patient experiences symptoms.[28] This explanation is strengthened by the outcomes of an RCT with relatively young patients treated with fludarabine (+/- cyclophosphamide).[10] In concordance with our results, it showed that CLL patients receiving treatment had a significantly impaired HRQoL on all functioning scales as well as on fatigue, nausea, and all single-items scales with the exception of pain, compared to a norm population. However, the baselines scores of these patients were similar or even worse than the scores twelve months after starting treatment, suggesting that the symptoms of disease affects HRQoL rather than therapy. On the other hand, our results also showed that patients receiving treatment scored lower than the norm population even after treatment had ended and symptoms are likely to be reduced. Therefore, we assume the poorer HRQoL among treated patients is caused by a combination of treatment effects and symptoms of active CLL. This hypothesis is confirmed by the results of a survey performed in 2006, where physical en functional well being and fatigue were related to both stage and treatment. HRQoL scores were lower among individuals with advanced stage disease.[29]

Remarkably, patients treated with chlorambucil reported lower scores on physical and social functioning, dyspnoea and fatigue than patients receiving other chemo-/immunotherapy. In contrast to our findings, are the results of a previous RCT that showed that during treatment patients receiving fludarabine, particularly FC, reported more HRQoL impairment compared with patients receiving chlorambucil, on role/social functioning and fatigue.[11] These differences resolved after completing therapy. There are several explanations for the discrepancies. First of all, we assessed HRQoL in a population-based setting that includes elderly and/or frail patients and patients with significant comorbidities, resulting in a representative subset of CLL/SLL patients receiving standard care, whereas patients with significant comorbidities or a short life expectancy were excluded from the trial.[30] Second, due to the observational nature of our study, the results might be biased by confounding by indication, i.e. elderly and/or frail patients with a poorer HRQoL being more likely to be treated with chlorambucil. However, we adjusted for age and comorbidity in the analyses and no statistical differences were observed in age, number of comorbidities, sociodemographic or clinical characteristics between patients treated with chlorambucil and from the other

chemo group. Third, the information provided to patients in a RCT is probably more elaborate and uniform than in a population-based setting. In the latter situation patients who receive a 'simple' oral treatment (chlorambucil) might receive less information than patients who are frequently hospitalized to receive 'complex' intravenous chemo-/immuno-therapy. Receipt of less information has been associated with lower HRQoL.[31]

In conclusion, despite the cross-sectional design of our study, this large population-based study with high patient response rates and detailed information about treatment, gives a quite representative overview of the symptoms and HRQoL that patients with CLL/SLL experience in all phases of disease.

The recent success in prolonging survival might lead to adjustment of the current guidelines regarding starting treatment in asymptomatic patients. However, drastic and long-lasting effects of starting treatment in CLL/SLL patients on HRQoL can not be excluded, whereas active surveillance does not seem to provoke worrying, anxiety, or depressive symptoms. Drastic, long-lasting negative effects of starting treatment on HRQoL can not be excluded, whereas active surveillance does not seem to provoke worrying, anxiety, or depressive symptoms. Further elaborate research into the impact of starting therapy on HRQoL is needed, especially in patients that are underrepresented in most clinical trials. Specifically, a larger cohort, which allows the comparison of more treatment groups and a design with questionnaires on specific moments (e.g. at diagnosis, 6 and 12 months after diagnosis, at start therapy, etc.) are preferable. Its results should be thoroughly considered during revision of treatment guidelines, as the gain in survival time by starting (a certain type of) treatment should outweigh the possible negative impact of it on patients HRQoL.

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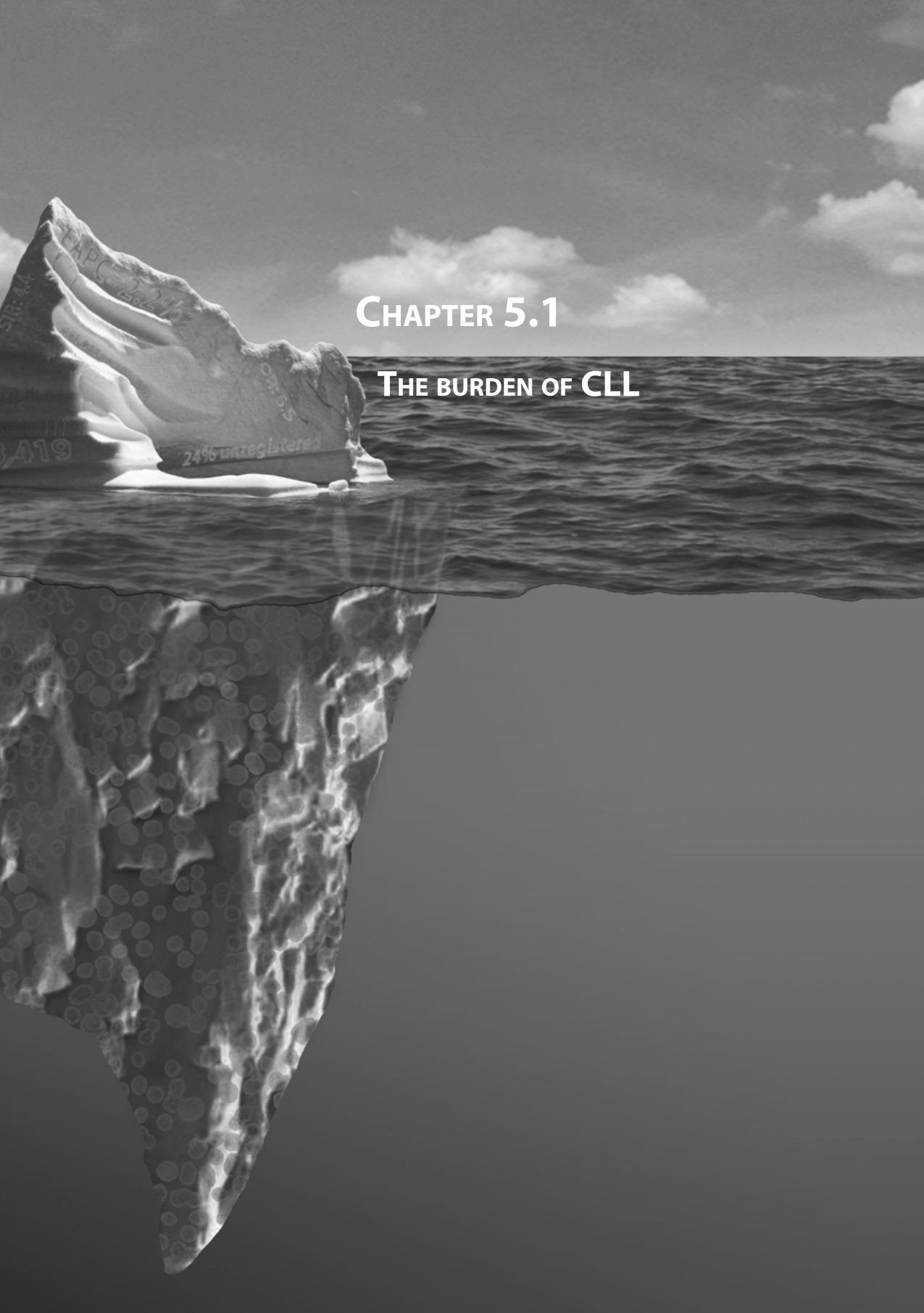
Chapter 5.

General discussion



Chapter 5.1

The burden of CLL

In the first paragraph of this chapter, I will discuss the outcomes of the studies in this thesis and their consequences. In the second paragraph guidelines for a proper population-based registry are presented.

One of the objectives of the studies described in this thesis was to investigate the burden of CLL. Burden was expressed as 1) incidence, 2) risk of multiple malignancies, 3) mortality and 4) impact on Health-Related Quality of Life (HRQoL).

The overall age standardised incidence rate in the Netherlands in the period 1989-2008 was estimated around 3.8 per 100,000, which is in accordance with European data.[1] This is probably an underestimation of 20-30% due to underregistration, the actual incidence is likely to be 4.5 – 5 per 100,000. The underestimation is mainly caused by the fact that CLL is one of the few malignancies that do not require pathological confirmation. [2]

We found that the incidence in the Netherlands increased for females aged 50–64 years (from 3.6 per 100,000 person-years in 1989 to 4.3 in 2008).[3] We hypothesize that this is the result from increased detection of CLL among cancer survivors. Cancer survivors undergo frequent medical check-ups that could expose asymptomatic CLL coincidentally.

The gradual implementation of the breast cancer screening programme in the Netherlands started in 1990. This led to an increase of the number of breast cancer survivors, i.e. middle-aged women with increased risk of detection of CLL.[4]

When we assessed the risk of CLL following the diagnosis breast cancer, we found that cancer survivors had indeed a 70% higher risk to be diagnosed with CLL than the general population.[5]

When analysing CLL following all earlier primary malignancies (EPM), we found that cancer survivors in general had a 90% higher risk to be diagnosed with CLL than the general population. In the first year after diagnosis we found a more than four-fold increased risk of CLL (Standardized Incidence Ratio (SIR): 4.4; 95%Confidence Interval (CI): 4.1-4.8), however no increased risk was observed after excluding synchronous cases (i.e. CLL diagnosed within three months after diagnosis of EPM) . Therefore, increased detection (due to intensive clinical check-ups after/around diagnosis of the EPM) seems to be the main cause for the increased risk of CLL among cancer survivors. However, possible shared risk factors between prostate cancer or skin cancer and CLL cannot be excluded as for these malignancies a significantly increased SIR was found after exclusion of synchronous CLL.

Analyses of T-cell malignancies in CLL patients (i.e. CLL being the first primary malignancy), resulted in increased standardised incidence ratios when compared with both the general population as well as all cancer survivors, ruling out increased detection as main cause. We hypothesize that CLL cells interact with T-cells in the microenvironment, facilitating malignant transformation.

Survival rates of CLL patients increased modestly. From 1989 to 2008, five-year relative survival increased from 61% to 70% in males and from 71% to 76% for females.

The aforementioned underregistration affects survival rates negatively. In our study where we retrieved data from all patients in two hospitals who were tested and/or treated for CLL in 2009 by using administrative codes and flow cytometry results, underregistration resulted in an underestimation of 6% points of the 5-year crude survival rate. After inclusion of newly registered patients, the survival rate increased from 72% to 78%. This could not solely be explained by the larger proportion of Rai 0 patients among the newly registered, as we found similar results within this group of patients; newly registered Rai 0 patients had a 5-year survival of 90%, whereas previously registered Rai 0 patients had a 5-year survival of only 76%.

A stage shift towards earlier stages (resulting from earlier detection) and/or better supportive care could explain the increasing survival rates rather than improved systemic treatment, as life-prolonging therapies were not available during the study period. It was not until 2010 that the CLL 8 trial showed improvement of survival (3-year progression free survival of 65% compared with 45%, 3-year overall survival of 87% versus 83%) after addition of a monoclonal antibody to chemotherapy in physically fit CLL patients[6]; in 2014, the CLL 11-trial did the same in patients with co-morbidities.[7]

These recent successes of the new treatment options may however have a downside. Our assessment of Health-Related Quality of Life (HRQoL) in a population-based setting showed that CLL-patients ever treated reported significantly poorer HRQoL than the norm population ($p<.01$ with large clinically important differences). Interestingly, no differences were observed between the norm population and patients under active surveillance. They might not have experienced symptoms of the disease yet. However, based on the results, long-lasting negative effects of starting treatment on HRQoL cannot be excluded, whereas active surveillance does not seem to provoke worrying, anxiety, or depressive symptoms too much. This should be taken into account in case of estimations of cost-effectiveness. Further research into the impact of starting therapy on HRQoL is needed, especially in patients who are underrepresented in most clinical trials, to discriminate between the effects of the onset of active disease and the resulting initiation of treatment, so physicians can make well informed decisions by balancing the impact of the therapy on HRQoL against the impact of active disease. We recommend comparative effectiveness research, combining RCTs and observational studies, to evaluate the pro's and cons of the therapeutic options, as new, promising therapies might be associated with a higher frequency of adverse events,[6,7] which can affect HRQoL negatively. The observational research is best to be based on registries like PHAROS, in which the collection of clinical, HRQoL and resource use data is combined. When the recent success in prolonging survival results in the development/adjustment of (new) guidelines regarding starting therapy in CLL-patients, the results of population-based HRQoL-studies should be taken into account. The same goes for resource use. As the costs of the CLL are not solely determined by the costs of (expensive) chemo(immuno-)therapy, inpatient days for other reasons than administration of chemo(immuno-)therapy are a main

cost driver too,[8] observational data concerning costs are required for proper policy making as well.

In conclusion, the prevalence of CLL (which is estimated to be about 5.900 patients in the Netherlands, i.e. about 65 patients per hospital on average) substantially underestimated, as both incidence and survival rates appeared to be negatively affected by underregistration of (mainly early stage) CLL-patients. The prevalence is expected to increase in the near future, as the number of cancer survivors in general (who have an increased risk of detection of CLL) are increasing. Furthermore, recently two trials showed improvement of survival of patients requiring treatment due to new therapeutic options.

Besides the increase in survival, the new therapeutic options will also result in higher costs (also by sometimes higher frequency of adverse events)[8], whereas the effect of starting therapy on HRQoL is not known yet.

Alongside the developments in the therapeutic area, insight into the pathogenesis[9] and the mechanisms causing heterogeneity is increasing. New techniques, such as next generation sequencing, have expanded the knowledge of the genomic alterations in CLL.[10, 11] A study among 3490 European CLL patients showed that NOTCH1 mutations, SF3B1 mutations and TP53 aberrations correlate with shorter time-to-first-treatment treatment-in naive Binet stage A cases.[12] A Spanish study with 587 patients revealed that TLR/MYD88 mutations identify a population of young CLL patients (median age: 47 years; range: 32 to 72 years and 83% younger than age 50 years at diagnosis). with favourable outcome.[13] Queiros et al. suggested a new categorization of CLL patients into three subgroups with differential clinico-biologic features and outcome, based on epigenetic biomarkers. [14]

These developments allow a more personalized therapeutic approach.
Evaluation of the new diagnostic and treatment strategies also demand proper population-based research to show the whole spectre of disease which requires corresponding registration of CLL. In the next chapter, guidelines for such a registry are presented.

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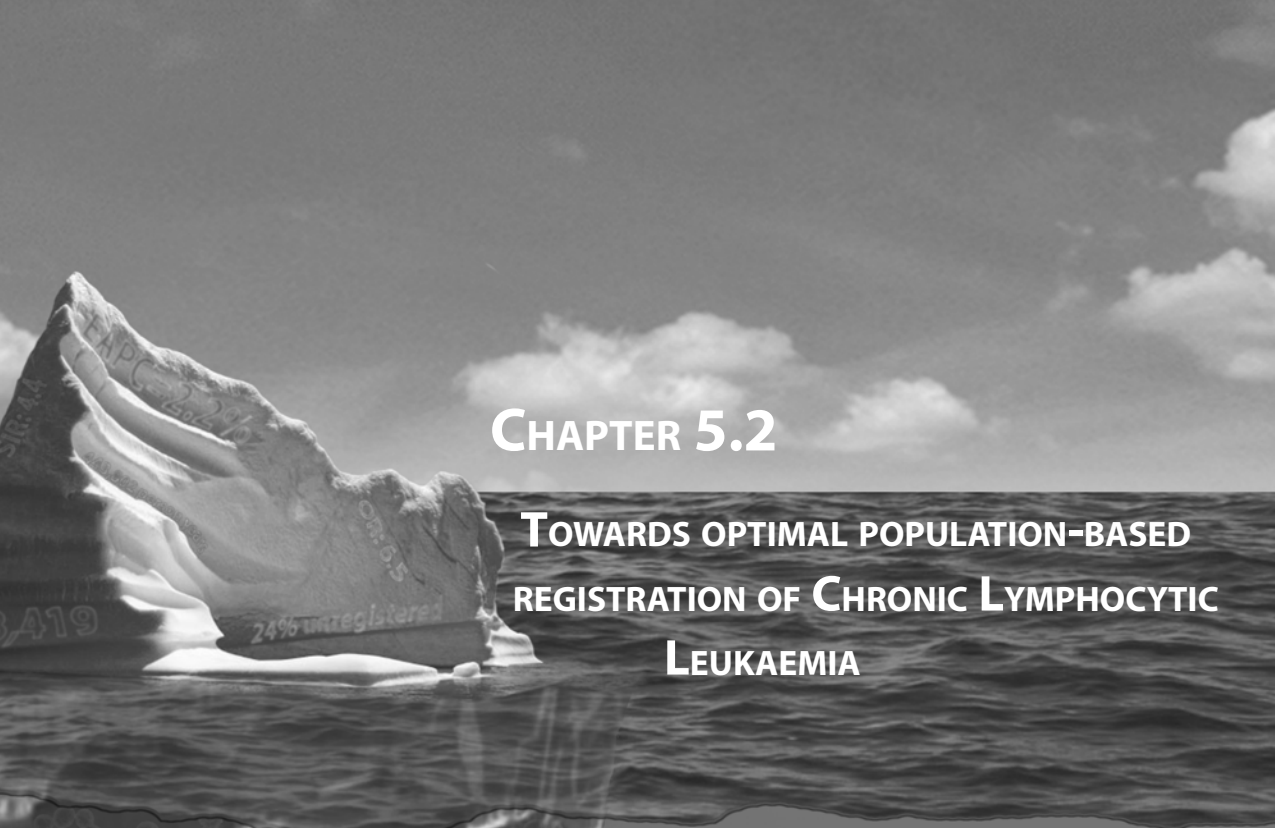

Chapter 5.2

Towards optimal population-based registration of Chronic Lymphocytic Leukaemia

E.C. van den Broek,
M. Brink,
A.P. Kater,
E.F.M. Posthuma,
L.V. van de Poll-Franse,
J.W.W. Coebergh

(Submitted)

Introduction

Chronic Lymphocytic Leukaemia (CLL) is the most common type of leukaemia in adults in western countries, both in terms of incidence and prevalence. The incidence in Europe is estimated to be 4.9 per 100,000 person years.[1] Current guidelines decree a wait-and-see policy for newly diagnosed cases unless or until there is evidence of active disease, as defined in International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) guidelines.[2] Relatively young and fit patients are mostly treated with FCR, CHOP-R and CVP-R. Fit patients with a p53 mutation or Del 17p are candidates for alemtuzumab containing therapies and even allogeneic stem cell transplantation. Elderly and frail patients often receive chlorambucil, with or without an anti-CD20 monoclonal antibody. [3]

Currently, new promising therapies for CLL are (about to be) introduced and treatment goals are about to change from minimising symptoms towards prolonging survival.[4, 5] Furthermore, variation in treatment increases as new insights in the heterogeneous course of the disease leads to more personalized medicine.[6]

Population-based research is essential to evaluate the (cost-)effectiveness of new treatments and diagnostic and prognostic tests. This requires valid registry data, however CLL has been shown to be underreported in cancer registries.[7, 8]

The unregistered cases are mainly early-stage asymptomatic, thus resulting in unrepresentative data. This might influence health resource planning; these patients do not require expensive treatment, but visit the internal/haematology outpatient clinic about every three months. Furthermore, the number of patients requiring treatment is often estimated as a proportion of all prevalent patients. So an underestimated prevalence could lead to miscalculation of the expected costs. Underregistration could also hamper proper etiological research, as risk factors can remain unrevealed when an unrepresentative sample of the patients is studied. Furthermore, it may lead to suboptimal treatment choices, when physicians expect the prognosis to be worse than it actually is.[9]

Completeness of a registry is not only about capturing all cases. It also concerns meaningful registration of all variables that are required (and availabe) for proper analyses of e.g. survival.

We feel the current underregistration and bias of CLL in most registries is a serious problem as the fast developments in therapy and stratification urge for more complete and reliable population based data. More accurate numbers concerning incidence, survival, stage distribution and treatment (effects) should be available for resource planning, policy making and (representative sampling) in research.

This paper points out the necessity for complete recording of CLL, so that the resulting population-based data may reliably reflect the incidence and are representative for the entire patient population. It also provides an overview of pitfalls that can be encountered when recording or analysing CLL-data as this malignancy behaves differently the most cancers on many points. Finally, recommendations are given for the collection of both clinical and quality of life data.

In order to come to recommendations for more complete useful population based registries concerning CLL in this paper, we evaluate

- existing literature on observational CLL data; including articles concerning underregistration[7,8], existing ENCR rules (summarized by Gavin et al.[10]), the Haemacare manual,[11] and current rules for coding from the Netherlands Cancer Registry (NCR) as well as the Hematopoietic and Lymphoid Database from the Surveillance, Epidemiology, and End Results (SEER) Program from the United States.[12]
- our assessment of completeness for CLL of the Netherlands Cancer Registry (NCR) in two large community hospitals
- analyses of the availability of the variables collected in the PHAROS- and PROFILES-registries. PHAROS is a supplement to the NCR, and records details on stage, (response to) treatment and adverse events of patients with haematological malignancies diagnosed between January 1st, 2004 and January 1st, 2011 in an area covering approximately 40% of the Dutch population.[13] PROFILES is an registry annexed to the Eindhoven Cancer Registry for the study of the physical and psychosocial impact of cancer and its treatment in a dynamic, growing population-based cohort of both short and long-term cancer survivors with additionally a control cohort of approximately 2000 persons from the general population.[14]

Evaluation

Coverage

Most cancer registries collect cancer cases by data from pathology departments, sometimes supplemented with hospitalization data. The same goes for the Netherlands Cancer registry (NCR) that receives notifications of all newly diagnosed malignancies in the Netherlands by the Dutch Pathology Registry (PALGA)[15] on a regular basis, and from the national registry of hospital discharge, once a year.

Unlike the majority of other malignancies, the definite diagnosis of CLL does not require pathological confirmation. According to International Workshop on Chronic Lymphocytic Leukaemia guidelines,[2] flow cytometric analysis of a blood sample is needed, usually done in clinical chemical laboratories.[16] Currently, biopsies are only indicated in case of doubt of the diagnosis, when transformation to Richter's disease is suspected or in case of cytopenia.[2] Hence, only very few cases of CLL in the Netherlands are signalled by PALGA.

In addition, most newly diagnosed CLL patients do not require treatment for their disease at the time of diagnosis and the disease can be managed at outpatient departments. Hospitalisations may be only required in case of severe symptoms and/or the necessity to start systemic therapy. So the national registry of hospital discharge is also insufficient for capturing all CLL cases.

To assess the completeness of the NCR, we retrieved data from all patients who were tested and/or treated (including those under active surveillance) for CLL in 2009 using administrative codes and flow cytometry results. Of 482 CLL cases that were reviewed, 117 (24%) were not (yet) registered in the NCR.[9]

Incidence date

Due to the long indolent course of CLL, there is a possible delay in detection, which makes it difficult to determine the exact clinical onset of the disease. The most consistent way to register onset date is to use the date of the first flow cytometric analysis that revealed a monoclonal B-cell population of at least $5x10^9$ lymphocytes/L with the immunophenotype CD5, CD19 and CD23 positive. In contrast to the ENCR[10], we advise against adaption of the incidence date if an event of higher priority (such as pathological confirmation or hospitalisation due to CLL) occurs, as these events mark the worsening of the disease, not the diagnosis. This approach is in line with the Haemacare guidelines[a].[11]

Registration of multiple notifications

The WHO classification and ICD-O-3 no longer distinguishes between CLL and SLL. We therefore recommend to follow the SEER program[12]; both diagnoses are recorded as M-9823/3, Currently, the code used in European registries to indicate SLL (M-9670/3) is a repository for several types of small cell lymphoma, not enabling a distinction in analyses between SLL and other small cell lymphomas. If both CLL and SLL are coded with the same morphology code, a distinction is still possible based on topography code (C42 for CLL and C77 for SLL).

When a CLL patient is also diagnosed with high-grade non-Hodgkin lymphoma, B-cell Prolymphocytic Leukaemia, Hodgkin lymphoma, or Acute Leukaemia 3 months or more after the CLL was diagnosed, this should be regarded as a transformation[17] and the morphology and date of diagnosis should not be adjusted, nor should a new malignancy be recorded. According to ENCR guidelines[10], when a transformation occurs within 3 months after the diagnosis of CLL, the morphology code of the transformed malignancy should replace that of CLL and be recorded as the first primary. Date of diagnosis remains unchanged as that of detection of the CLL.

All other (haematological) malignancies should be recorded as second primary malignancies (SPM). When analysing CLL as a SPM, one should be aware of the long latent phase of CLL, often present when the other malignancy was developing, possibly symptomless and therefore unnoticed. The diagnostic process of the other cancer usually initiates check-ups that coincidentally reveal CLL, suggesting it to be the second malignancy, while it was actually the first. This also illustrates another pitfall: a diagnosis of another malignancy (or other chronic disease, trauma or viral disease) increases the chance of a subclinical CLL being detected. When evaluating the true risk of CLL coinciding with another malignancy one should try to correct for the aforementioned detection bias by comparing the incidence rates in the study population with the incidence rates in cancer survivors instead of entire

[a] *The Haemacare guidelines are a coding manual for haematological malignancies, prepared by twelve experts (senior physicians, epidemiologists and onco-haematologists) from France, Finland, Italy, Spain, Switzerland, and the Netherlands, to promulgate standard rules for the registration of haematological malignancies for use by population-based cancer registries*

national or regional populations. CLL diagnosed less than 3 months after the diagnosis of the other malignancy should be regarded as synchronous, rather than metachronous. Often an interval of 6 months is used to discriminate synchronous from metachonous cancers. However, CLL is much easier detected coincidentally (during a blood count) than most solid tumours that often require a form of imaging to be detected in a subclinical phase.

Most relevant and feasible clinical items to register

We consider stage an important variable. However, the PHAROS registry showed that in half of the patient files, neither Rai nor Binet stage at diagnosis is recorded. Therefore, we recommend replenishing the variable 'stage' with the variables:

- Number of enlarged lymphnode stations,
- hepatomegaly (yes/no/not mentioned),
- splenomegaly (yes/no/not mentioned),
- haemoglobin (in mmol/L or gram/dl) ,
- thrombocyte level (number of thrombocytes x 10^9/L).

For the last two items, we recommend to let the clerks record laboratory results rather than interpret whether or not the results were below or above normal.

As treatment choice is not only based on stage and age, but also on frailty, it is recommended to register co-morbidities (by means of the Charlson Comorbidity Index[18] or its adapted form used by the ECR, see Table 1) and/or Karnofsky score or WHO-performance status.

Table 1: *Classification of co-morbidity, according to an adapted version of Charlson and colleagues[18]*

Class	
Previous malignancies	except basal cell skin carcinoma and carcinoma in situ of the cervix
Pulmonary diseases	e.g. COPD, CARA, emphysema
Cardiovascular diseases	e.g. Myocardial infarction, cardiac decompensation, angina pectoris, intermittent claudication, abdominal aneurysm, peripheral arterial disease, hypertension, cerebrovascular accident
Gastro-intestinal diseases	e.g. Crohn's disease, ulcerative colitis, esophagitis, pancreatitis
Liver diseases	e.g. cirrhosis, hepatitis
Kidney diseases	e.g. chronic glomerulonephritis, pyelonephritis
Connective tissue diseases	e.g. Besnier Boeck disease, Wegener's disease, systemic lupus erythematosus (SLE), Rheumatoid arthritis (only severe)
Diseases of the nervous system	e.g. Alzheimer 's disease, hemiplegia, multiple scleroses
Endocrine disorders	e.g. Diabetes mellitus, Addison's disease, Hyperthyroidism
Bleeding disorders	e.g. Von Willebrand's disease
Infections	e.g. AIDS, Tuberculosis

Although it would be very interesting to evaluate new, possible prognostic factors in a population-based setting, the imperfect retrospective nature of registries complicates this. Outside the trial-setting, these prognostic factors have often not yet been validated.[6] And if assessed, it is often not at diagnosis but just preceding the start of therapy, as for example is recommended for cytogenetics in both the IWCLL-guidelines[2] and the HOVON guidelines.[19] Hence, this item remaines unknown in most recently diagnosed patients. Should registries record possible prognostic factors that are not yet validated and recommended in clinical daily practice? Registries can be useful in assessing utilisation patterns, often changing over time, which can help at the evaluation and fine-tuning of new guidelines concerning diagnostic and prognostic tests. So registration of prognostic factors, can be considered, once they are being introduced in daily practice which can show the great variation among and between early and late adaptors of new technologies.

If trial participation is registered, it is easier to link the registry data (with long follow-up time) to RCT-data (with more clinical parameters, such as the aforementioned possible prognostic factors).

The cause of death of CLL-patients is often so multi-dimensional, that even well-trained clerks find it hard to discern the direct and/or underlying cause from the patient files and to document this in a consistent manner. All in all, if one is interested in disease specific survival it is generally more useful to calculate relative survival rates.[20]

Evaluation of treatment choices, outcomes and adverse events (and the subsequent resource use) in a population-based setting seems worthwhile as a large proportion of patients (such as elderly and/or comorbid patients) are often excluded from randomized trials.[3] Adverse events and resource use are also required for cost-effectiveness assessment: a comparative costs analysis of unselected CLL patients in the Netherlands learned that the main cost driver for CLL was inpatient days for other reasons than administration of chemo(immuno-) therapy, e.g. blood transfusion, pneumonia, other infections, or fever of unknown origin .

However, population-based registration of treatment data is more complicated for CLL than for most other malignancies, due to the long periods (varying from months up to decades) prior and between actual treatment. This requires multiple registration moments. It is recommended to limit the items to those that are crucial to answer the -often rough - research questions at hand and cannot be obtained through other sources. Sometimes, it might be better to only record details of a representative subsample, to avoid getting bogged down in details and time consuming registration.

Population-based research of Health-related quality of life

The long and variable time prior and between active treatments also complicates longitudinal HRQoL-research in CLL patients.

When one chooses to collect data at fixed moments (at diagnosis, 6 months after diagnosis, 1 year after diagnosis, etc.) one should realise this will yield a very heterogeneous responding population with regard to presence of symptoms, disease stage, treatment phase and

individual awareness. However, a design with variable intervals (e.g. at diagnosis, at start of treatment, shortly after treatment etc.) is almost impractible and requires the intense cooperation of the clinical staff, which endangers complete coverage and increases the risk of inclusion bias.

A web-based registry, such as PROFILES[21], also allows patients and physicians to have a say in both the frequency of and the intervals between data collection, as patients are able to log in and fill out a questionnaire when they feels it is relevant and/or when their physician requests this, and might partly solve this problem.

International collaboration

Although CLL is the most is the most common leukaemia in the Western hemisphere, incidence rates are relatively low compared to other cancers. Furthermore, most patients do not require treatment for a long period after diagnosis. This makes it difficult to compare different treatment regimens, as the number of patients in the treatment groups is often too low for proper statistical estimations. Registries should therefore primarily document variation in treatment strategies. It is obvious that international collaboration like the European Research Initiative on CLL (ERIC)[b] may be useful.

Harmonisation of registration rules, study questions and laboratory methods, as was already recommended by ERIC[22], is a prerequisite for reliably merging datasets.

Conclusion

We are witnessing a new era for CLL, where new prognostic markers allow better classification of CLL patients with regard to progression and outcome, and new therapeutic options shift treatment goals from minimisation of symptoms towards prolongation of (progression-free) survival. To guarantee that all patients benefit maximally from these developments, the accuracy of the prognostic models as well as the (cost-)effectiveness and tolerability of the new therapies and the variation in utilisation of both tests and therapies in daily clinical practice should be evaluated. A robust population based registry is needed, and extra efforts need to be made to find more subclinical cases. We recommend registration of a limited set of data on multiple moments and, if required for answering a specific study question, supplementation with detailed data collected in a well defined cohort.

[b] *ERIC is a European organization, devoted to improve the outcome of patients with CLL and related diseases and open to all working in this field, to achieve faster progress by open communication between study groups, physicians and scientists*

Recommendations

- In addition to pathology data, hospital records and death notifications, registries should use data on blood and flow cytometry from haematology and/ or clinical chemical laboratories for a more complete coverage of CLL patients
- The date of the first flow cytometric analysis that revealed a monoclonal B-cell population of at least $5x10^9$ cells/L is to be registered as the onset date. It should not be adapted after occurrence of an event of higher priority (such as pathological confirmation or hospitalisation due to CLL).
- ICD-O-3 morphology code M-9823/3 should be used to register both CLL and SLL, combined with topography code C42 for CLL and C77 for SLL.
- When a CLL patient is diagnosed with another haematological malignancy, the recently developed ENCR guidelines regarding transformation should be followed.
- When evaluating the true risk of CLL coinciding with another malignancy, one should consider comparing the incidence rates in the study population with the incidence rates in (other) cancer survivors instead of using the entire nations population, to correct for detection bias.
- The registry should include the following items:
  - Number and site of enlarged lymphnode stations,
  - hepatomegaly (yes/no/not mentioned),
  - splenomegaly (yes/no/not mentioned),
  - haemoglobin (in mmol/L or gram/dL) ,
  - thrombocyte level (number of thrombocytes x 109/L),
  - co-morbidities,
  - Karnofsky score or WHO-performance status,
  - trial and cohort study participation
- New prognostic markers that are not yet recommended in clinical daily practice can be registered to describe variance in utilisation. The evaluation of their predictive value is however often hampered by low numbers.
- Registration of adverse events and resource use are required for cost-effectiveness assessment of new treatments as the main cost driver for CLL is inpatient days for other reasons than administration of chemo(immuno-) therapy.
- We prefer to register a limited number of items at multiple registration moments rather than to collect a large set of items at one point in time. Detailed data required to answer a specific study question are preferably colleted in a limited period and/ or part of the population.
- In population-based HRQoL-research, a web-based registry which enables data collection at both fixed and variable intervals can be useful to reduce the heterogenity in the responding population with regard to presence of symptoms, disease stage, treatment phase and individual awareness.
- International collaboration to achieve a large enough cohort for analyses of different treatment regimens and/or new prognostic markers seems obvious.

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Summary

Introduction

Chronic Lymphocytic Leukaemia (CLL) is the most common type of leukaemia in adults in industrialized western countries, both in terms of incidence and prevalence. This haematological malignancy is often asymptomatic and can remain undetected for many years. Therefore, the current knowledge about CLL is likely to be affected by the so-called "iceberg-phenomenon". In chronic disease epidemiology, this term is used to describe the situation where the number of known, clinical cases of a disease (i.e. the visible tip of the iceberg) is outweighed by those that are still in an unknown, subclinical phase (the larger submerged part of the iceberg).

In this thesis, the findings resulting from exploration of the CLL-iceberg are described within the framework of the Population-based HAematological Registry for Observational Studies (PHAROS) project. In this project, a dataset (supplemental to the Netherlands Cancer Registry) was established in an area covering approximately 40% of the Dutch population in order to evaluate treatment variation and impact of new drugs and their cost effectiveness in a population based setting.

Incidence

Based on population-based data from the Netherlands Cancer Registry, the incidence rate of CLL in the Netherlands between 1989 and 2008 was found to be stable at 3.8 per 100,000 person years. This is in accordance with European data. Among Dutch males, the incidence rate was stable at 5.1 per 100,000 person-years. For females however, I saw an increase from 2.3 to 2.5 per 100,000 person-years, which was most pronounced in females aged 50-64 years (from 3.6 to 4.3 per 100,000 person-years) (**Chapter 2.1**).

These incidence rates are suspected to be underestimated due to underregistration of CLL in cancer registrations. The extent of underreporting of CLL in the Eindhoven Cancer Registry until 2014 held at Integraal Kankercentrum Zuid (IKZ), since 2014 at IKNL (Integraal Kankercentrum the Netherlands) is assessed in **chapter 2.2**. By using the administrative codes and data from the clinical chemical laboratory, patient data from all patients in two hospitals who were tested and/or treated for CLL in 2009 (both incident and prevalent cases) were retrieved. I found that 24% of the CLL cases were not (yet) registered in the ECR.
Survival

In the Netherlands, five-year relative survival increased from 61% in 1989-1993 to 70% 2004-2008 for males, and from 71% to 76% for females. This modest increase is possibly underestimated as the aforementioned underreporting concerns mainly patients with long survival rates. The registered patients had a crude 5-year survival of 72%. Inclusion of the unregistered patients (who had a crude 5-year survival of 90%) resulted in a crude 5-year survival of 78%. Data from the Population-based HAematological Registry for Observational Studies (PHAROS) enabled analyses based on stage at diagnosis. Part of the difference in survival could thus be explained by underregistration of mainly patients with Rai 0 CLL. After addition of the unregistered patients to the ECR, the proportion of patients with Rai 0 CLL increased from 59% to 67% ($p < 0.001$).

However, when analysing solely the Rai 0 patients, survival of unregistered patients (crude 5-year survival: 90%) remained higher than that of the registered patients (crude 5-year survival: 76%) (p=0.06).

When studying the trends in survival, one should also realise that the effect of the introduction of new therapies on survival of CLL patients is harder to visualise than in most other malignancies. Usually, trends in survival rates are calculated based on year of diagnosis (e.g. comparing patients diagnosed prior to the introduction of a new therapy to patients diagnosed afterwards). In most malignancies, this is appropriate as the year of diagnosis is often equal to the year therapy was started. In CLL however, the interval between diagnosis and start of treatment is often very long (up to years) and highly variable, causing spreading of the effect of new therapies over many years of diagnosis.

CLL IN RELATION TO OTHER MALIGNANCIES

The increasing incidence among females aged 50-64 described in **chapter 2.1** coincided with the introduction of mass screening for breast cancer which had a very high proportion of participating women. This led to the hypothesis the increase in incidence could be caused by increased detection rates of CLL among cancer survivors and/or newly diagnosed patients with cancer. Cancer survivors undergo frequent medical check-ups that could expose asymptomatic CLL coincidentally, resulting in a higher incidence of CLL among cancer survivors compared to the general population.

As the introduction of breast cancer screening increased the number of breast cancer survivors substantially, it resulted in a relatively large group of middle-aged women with increased risk of detection of CLL.

In **chapter 3.1**, the risk of CLL following earlier primary malignancies (EPM) is assessed. Overall, cancer survivors had a 90% higher risk to be diagnosed with CLL than the general population. In the first year after diagnosis, the Standardised Incidence Ratio (SIR) is 4.4; (95%Confidence Interval (CI): 4.1-4.8). No increased risk was observed after excluding synchronous cases (i.e. CLL diagnosed within 3 months after the FPM was diagnosed). Therefore, increased detection due to intensive clinical check-ups after/around diagnosis of the EPM seems to be the main cause for the increased risk of CLL among cancer survivors.

However, possible shared risk factors between CLL and prostate cancer or squamous cell skin cancer cannot be excluded, as for survivors of these malignancies an increased risk for CLL was found after exclusion of synchronous cases (SIR: 1.3; 95%CI: 1.1-1.5 and SIR: 2.3; 95%CI: 1.9-2.7, respectively).

Based on the results described in **chapter 3.2**, I suspect a direct causal relation between CLL and T-cell malignancies, where CLL cells interact with T-cells, in the microenvironment, facilitating malignant transformation.

To rule out increased detection as main cause of higher incidence, the incidence of T-cell malignancies among newly diagnosed CLL-patients registered in the Surveillance

Epidemiology and End Results (SEER) database in the USA was compared to that among all U.S. cancer survivors, instead of the general population. The risk among CLL patients was more than twofold higher than among patients with other malignancies (SIR 2.1; 95% CI: 1.7-2.7).

Health-Related Quality of Life in patients with CLL

In **chapter 4.1**, Health-Related Quality of Life (HRQoL) was assessed in a population-based setting, allowing inclusion of patients who are often underrepresented in randomized clinical trials. For this purpose, patient reported outcomes were collected within the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) Registry, which is linked to the Eindhoven Cancer Registry. Treatment data were extracted from the PHAROS-database.

Interestingly, no differences were observed between the norm population and CLL patients under active surveillance. Patients ever treated for CLL however reported significantly poorer HRQoL than the norm population ($p<0.01$ with large clinically important differences) and the patients under active surveillance ($p <.001$ with medium and small clinically important differences). Patients treated with chlorambucil reported the lowest HRQoL scores. The prevalence of fatigue among this group (81%) was almost twice as high compared to the active surveillance group (42%) ($p<0.01$), and also higher than those who underwent other chemo-/immunotherapy (63%), although not statistically significant.

Conclusion

In **chapter 5.1**, I conclude, that the prevalence of CLL is currently substantially underestimated, as both the incidence and survival rates appeared to be negatively affected by underregistration of (mainly early stage) CLL-patients.

The current developments in the field of CLL (such as the expected increase in incidence due to increased detection among cancer survivors and the introduction of new, expensive therapies with possible more adverse events) demand a more representative population-based registry, with data concerning, stage, treatment and HRQoL. In **chapter 5.2**, recommendations are provided to achieve such as registry, which is crucial in evaluating the (cost-)effectiveness of both the new therapies and new prognostic models that are currently (about to be) introduced.

Samenvatting

Introductie

Chronische Lymfatische Leukemie (CLL) is de meest voorkomende vorm van leukemie onder volwassenen in geïndustrialiseerde westerse landen, zowel qua incidentie als prevalentie. In Nederland betreft het ruim 750 nieuw gediagnosticeerde patiënten per jaar. Deze hematologische maligniteit verloopt vaak asymptomatisch en kan vele jaren onontdekt blijven. Door dit "ijsbergfenomeen" blijft de huidige kennis over CLL waarschijnlijk beperkt. In de epidemiologie wordt deze term gebruikt om de situatie te beschrijven waarin het aantal bekende, klinische gevallen van een chronische ziekte (de zichtbare top van de ijsberg) slechts een fractie is van het aantal patiënten dat zich in een onbekende, subklinische fase bevindt (het grotere deel van de ijsberg bevindt zich onder water).

In dit proefschrift worden de bevindingen van de verkenning van de CLL-ijsberg beschreven, binnen het kader van het Population-based HAematological Registry for Observational Studies (PHAROS) project. In dit project werd een dataset verwezenlijkt (aanvullend op de Nederlandse KankerRegistratie (NKR)) in een gebied dat ongeveer 40% van de Nederlandse bevolking dekt, om de variatie in behandeling en het effect van nieuwe therapieën en hun kosteneffectiviteit te evalueren in een population-based setting.

Incidentie

Op basis van population-based gegevens van de NKR, bleek de incidentie van CLL in Nederland tussen 1989 en 2008 stabiel te zijn; 3,8 per 100.000 persoonsjaren. Dit komt overeen met Europese aantallen. Onder Nederlandse mannen bleef de incidentie stabiel op 5,1 per 100.000 persoonsjaren. Onder vrouwen zag ik echter een toename van 2,3 tot 2,5 per 100.000 persoonsjaren, die het sterkst was onder vrouwen in de leeftijd van 50-64 jaar (van 3,6 tot 4,3 per 100.000 persoonsjaren) (**Hoofdstuk 2.1**).

Deze incidentiecijfers zijn waarschijnlijk een onderschatting ten gevolge van onderregistratie van CLL in kankerregistraties. De omvang van onderrapportage van CLL in de Eindhoven Cancer Registry (ECR; tot 2014 beheerd door Integraal Kankercentrum Zuid (IKZ), sinds 2014 door Integraal Kankercentrum Nederland (IKNL)) is bepaald in **hoofdstuk 2.2**. Door gebruik te maken van DBC-codes en gegevens van het klinisch chemisch laboratorium, werden in twee middelgrote ziekenhuizen patiëntgegevens verkregen van alle patiënten die daar in 2009 werden getest op en/of behandeld voor CLL (zowel incidente en prevalente gevallen). Ik ontdekte dat 24% van de CLL-patiënten (nog) niet geregistreerd was in de ECR. Vergelijkbaar onderzoek bij andere registraties resulteerde in dezelfde uitkomsten (27% en 38%). In de literatuur wordt echter zelden gecorrigeerd voor onderregistratie en wordt uitgegaan van de geregistreerde aantallen.

Overleving

In Nederland steeg de relatieve vijfjaarsoverleving (dit is het percentage patiënten dat vijf jaar na de diagnose nog in leven is, gecorrigeerd voor de verwachte sterfte die is gebaseerd op de Nederlandse populatie vergelijkbaar op basis van geslacht, leeftijd en kalenderjaar) van mannen met CLL van 61% in 1989-1993 tot 70% in 2004-2008, en van 71% tot 76% voor vrouwen. Deze bescheiden toename is mogelijk onderschat, aangezien de eerdergenoemde onderrapportage hoofdzakelijk patiënten met een lange overleving betreft. De geregistreerde

patiënten hadden een ruwe 5-jaarsoverleving ((dit is het percentage patiënten dat vijf jaar na de diagnose nog in leven is, zonder correctie voor de verwachte sterfte) van 72%. Inclusie van de ongeregistreerde patiënten (die een ruwe 5-jaarsoverleving van 90% hadden) resulteerde in een ruwe 5-jaarsoverleving van 78%. Gegevens uit het PHAROS-project maakten analyses mogelijk op basis van stadium bij diagnose. Een deel van het verschil in overleving kon verklaard worden door onderregistratie van hoofdzakelijk (79%) patiënten met Rai 0 CLL. Na toevoeging van de ongeregistreerde patiënten aan de ECR, steeg de proportie patiënten met Rai 0 CLL van 59% naar 67% ($p < 0.001$).

Echter, bij analyse van uitsluitend Rai 0 patiënten bleef de overleving van ongeregistreerde patiënten (ruwe 5-jaarsoverleving: 90%) hoger dan die van geregistreerde patiënten (ruwe 5-jaarsoverleving: 76%) ($p=0.06$).

Bij het bestuderen van trends in overleving, moet men zich realiseren dat het effect van de introductie van nieuwe therapieën op de overleving van CLL-patiënten lastiger te visualiseren is dan in de meeste andere maligniteiten. Doorgaans worden trends in overleving berekend op basis van diagnosejaar (bijv. een vergelijking tussen patiënten gediagnosticeerd vóór de introductie van een nieuwe therapie en daarna gediagnosticeerde patiënten). Voor de meeste maligniteiten is dit een geschikte aanpak, aangezien het diagnosejaar vaak gelijk is aan het jaar waarin de therapie gestart werd. Bij CLL is het interval tussen diagnose en start van behandeling echter vaak erg lang (oplopende tot jaren) en erg variabel, waardoor het effect van nieuwe therapieën uitgesmeerd wordt over vele diagnosejaren.

CLL IN RELATIE TOT ANDERE MALIGNITEITEN

De in **hoofdstuk 2.1** beschreven gestegen incidentie onder vrouwen in de leeftijd 50-64 viel samen met de introductie van het bevolkingsonderzoek borstkanker dat in Nederland een erg hoge deelname kent. Dit leidde tot de hypothese dat de stijgende incidentie veroorzaakt zou kunnen worden door verhoogde detectie van CLL onder kankeroverlevers en/of nieuw gediagnosticeerde patiënten met kanker. Kankeroverlevers ondergaan doorgaans frequente medische controles die een asymptomatische CLL bij toeval kunnen onthullen, resulterend in een hogere incidentie van CLL onder kankeroverlevers vergeleken met de algehele bevolking.

Doordat de introductie van het bevolkingsonderzoek het aantal borstkankeroverlevers substantieel verhoogde, resulteerde dit in een relatief grote groep vrouwen van middelbare leeftijd met een verhoogde kans op detectie van CLL.

In **hoofdstuk 3.1** wordt het risico op CLL na eerdere primaire maligniteiten (EPM) bepaald. In het algemeen hadden kankeroverlevers 90% meer kans om gediagnosticeerd te worden met CLL dan de algehele bevolking. In het eerste jaar na diagnose is de Standardised Incidence Ratio (SIR) 4.4; (95%Betrouwbaarheidsinterval (BI): 4.1-4.8). Na exclusie van synchrone gevallen (CLL gediagnosticeerd binnen 3 maanden na diagnose van de EPM) werd geen verhoogd risico meer gezien. Hierdoor lijkt verhoogde detectie ten gevolge van intensieve klinische controles rondom/na diagnose van de EPM de voornaamste oorzaak te zijn van het verhoogde risico op CLL onder kankeroverlevers.

Voor prostaatkanker en plaveiselcelcarcinoom kunnen mogelijke gedeelde risicofactoren met CLL echter niet worden uitgesloten, aangezien onder overlevers van deze maligniteiten ook een verhoogd risico op CLL werd gevonden na exclusie van synchrone gevallen (SIR: 1.3; 95%BI: 1.1-1.5 en SIR: 2.3; 95%BI: 1.9-2.7, respectievelijk).

Op basis van de resultaten beschreven in **hoofdstuk 3.2**, vermoed ik een direct causaal verband tussen CLL en T-cel maligniteiten, waar CLL-cellen een interactie aangaan met T-cellen in de micro-omgeving en maligne transformatie faciliteren.

Om verhoogde detectie als voornaamste oorzaak van een hogere incidentie uit te sluiten, werd de incidentie van T-celmaligniteiten onder nieuw gediagnosticeerde CLL-patiënten geregistreerd in de Surveillance Epidemiology and End Results (SEER) database in de Verenigde Staten vergeleken met de incidentie onder alle Amerikaanse kankeroverlevers, in plaats van met die van de algehele bevolking. Het risico onder CLL-patiënten was meer dan twee keer zo hoog als onder patiënten met andere maligniteiten (SIR 2.1; 95% BI: 1.7-2.7). Alles bijeen gaat het om ongeveer 15 patiënten met een T-celmaligniteit per 100.000 CLL-patiënten per jaar.

Kwaliteit van Leven van patiënten met CLL

In **hoofdstuk 4.1** werd de Kwaliteit van Leven (KvL; het functioneren van personen op fysiek, psychisch en sociaal gebied) bepaald in een population-based setting, die inclusie mogelijk maakte van patiënten die vaak ondervertegenwoordigd zijn in gerandomiseerde studies. Patiëntgerapporteerde uitkomsten werden verzameld binnen de PROFIEL-studie (Profiel is de vertaling van PROFILES dat staat voor Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship) die gekoppeld is aan de NKR. Behandelingsgegevens werden verkregen uit de PHAROS-database.

Opmerkelijk was dat er geen verschillen werden gezien tussen de normpopulatie en CLL-patiënten met een afwachtend beleid. Patiënten die ooit systemisch behandeld waren voor CLL rapporteerden echter een significant slechtere KvL dan de norm populatie ($p<0.01$ met grote klinisch relevante verschillen) en de patiënten met een afwachtend beleid ($p <.001$ met middelgrote en kleine klinisch relevante verschillen). Patiënten behandeld met chlorambucil rapporteerden de laagste KvL scores. De prevalentie van vermoeidheid in deze groep (81%) was bijna tweemaal zo hoog als in de groep met een afwachtend beleid (42%) ($p<0.01$), en eveneens hoger dan onder hen die andere chemo-/immunotherapie ondergingen (63%), dit was echter niet statistisch significant.

Conclusie

In **hoofdstuk 5.1**, concludeer ik dat de prevalentie van CLL (rond de 6000 patiënten in Nederland) momenteel substantieel onderschat is, aangezien zowel de incidentie als de overleving negatief beïnvloed bleken door onderregistratie van (hoofdzakelijk vroeg stadium) CLL-patiënten. De werkelijke prevalentie is waarschijnlijk hoger dan 10.000 patiënten.

De huidige ontwikkelingen in het veld, zoals de verwachte toename in incidentie ten gevolge van verhoogde detectie onder overlevers van andere vormen van kanker en de introductie van zowel nieuwe, dure, prognostische testen als tientallen nieuwe, tijdelijk kostbare therapieën (met mogelijk ook meer bijwerkingen) voor patiënten met actieve ziekte, vragen om een meer representatieve, population-based registratie, met gegevens betreffende stadium, behandeling en KvL, zoals ook in het PHAROS-project gerealiseerd. In **hoofdstuk 5.2** worden de volgende aanbevelingen gedaan om een degelijke registratie te bewerkstelligen:

- Naast pathologie-uitslagen, opnameverslagen en overlijdensregistraties, zouden registraties ook gegevens van hematologie en/of klinisch chemisch laboratoria (flow cytometry[1] uitslagen) moeten gebruiken voor signalering van CLL
- De datum van de eerste flow cytometrische analyse die een monoclonale[2] B-cel populatie van ten minste $5x10^9$ cellen/L laat zien, dient geregistreerd te worden als diagnosedatum. Deze hoeft niet aangepast te worden als er een gebeurtenis met een hogere prioriteit plaatsvindt (zoals pathologische bevestiging of opname ten gevolge van CLL).
- ICD-O-3 morfologie-code M-9823/3 dient gebruikt te worden voor de registratie van zowel CLL als Kleincellig Lymfocytair Lymfoom (SLL), in combinatie met ICD-O-3 topografie-code C42 voor CLL en C77 voor SLL.
- Wanneer een CLL-patiënt wordt gediagnosticeerd met een andere hematologische maligniteit, dienen de richtlijnen van de European Network of Cancer Registries (ENCR) met betrekking tot transformatie te worden gevolgd (Als er transformatie optreedt[3] binnen drie maanden na diagnose wordt de morfologie-code aangepast, treedt de transformatie na drie maanden op blijft de oorspronkelijke morfologie code staan. Als er een hematologische maligniteit van een andere klasse wordt gediagnosticeerd, dienen beide maligniteiten te worden geregistreerd.)
- Bij het bepalen van het werkelijke risico op CLL in combinatie met een andere maligniteit, dient de incidentie in de onderzoekspopulatie niet te worden vergeleken met de incidentie in de algehele bevolking, maar met de incidentie onder alle kankeroverlevers, om te corrigeren voor detectie bias
    - De registratie zou ten minste de volgende items moeten omvatten:
    - aantal aangedane lymfklierstations,
    - hepatomegalie en splenomegalie,
    - hemoglobine- en trombocytengehalte,
    - co-morbiditeiten (bijkomende ernstige ziekten),
    - Karnofsky score of WHO-performance status,
    - trial deelname

[1]) Flowcytometrie is een techniek voor het tellen en typeren van cellen in een vloeistof. Hierbij wordt er gebruik gemaakt van fluorescentie.

[2]) Monoclonaal betekent dat de kwaadaardige cellen identiek zijn, doordat ze het resultaat zijn van meerdere celdelingen van één originele kankercel.

[3])Bij transformatie ontwikkelt een indolente (niet-agressieve) hematologische maligniteit zich tot een agressievere maligniteit van dezelfde klasse.

- Het is beter een beperkt aantal items te verzamelen op meerdere momenten dan een grote set data op één moment te registreren.
- In population-based KvL-onderzoek kan een registratie via het internet handig zijn wanneer deze dataverzameling op zowel vaste als variabele intervallen mogelijk maakt en zo problemen door de sterk variërende tijd tot behandeling van CLL patiënten het hoofd biedt.
- Het verdient aanbeveling om internationale samenwerking te zoeken om zo een cohort samen te stellen dat groot genoeg is voor de analyses van verschillende behandelingsstrategieën.

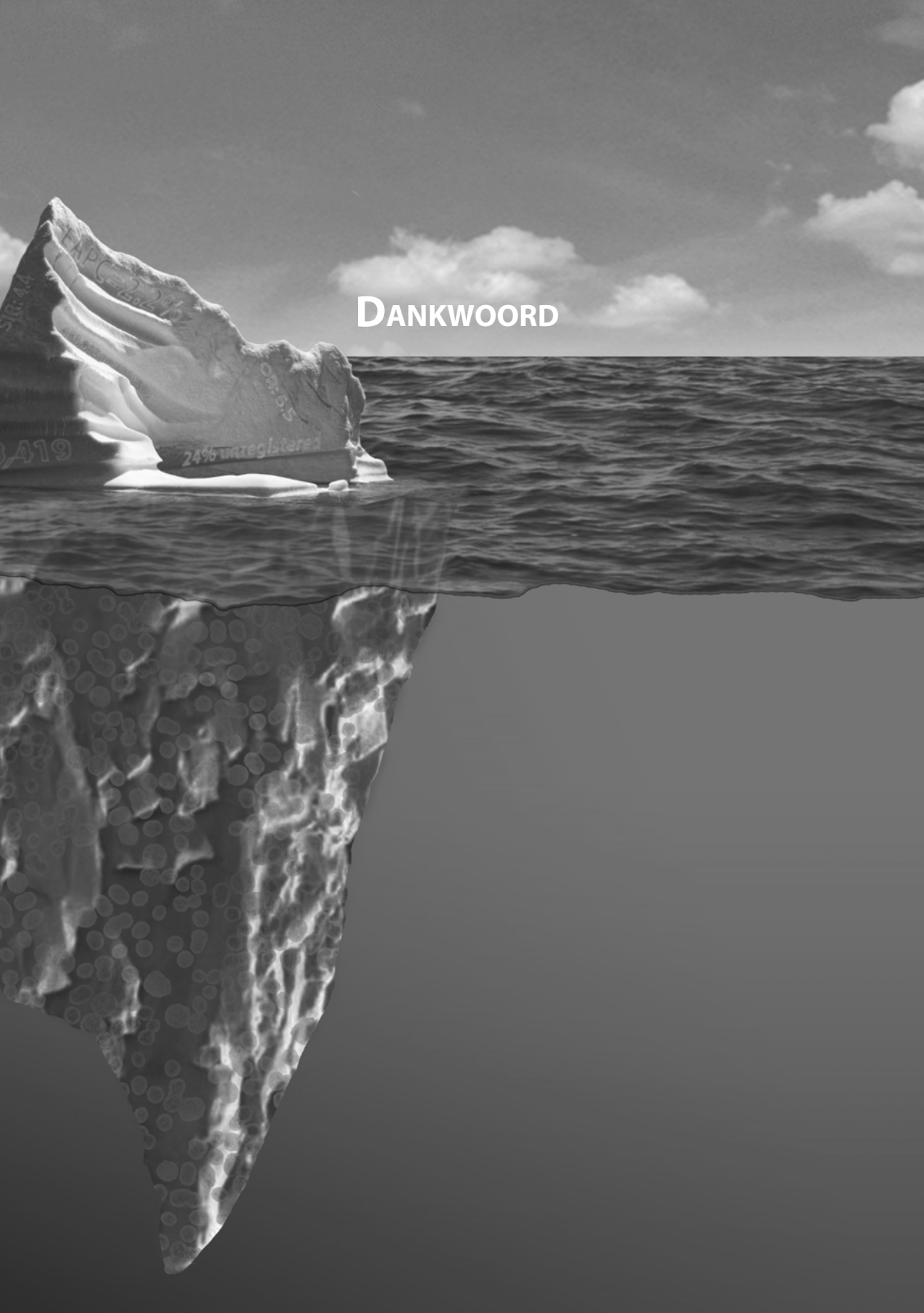
Dit is cruciaal voor een betekenisvolle evaluatie van (kosten-) effectiviteit van de vele nieuwe prognostische testen en therapieën[4] die op dit moment (op het punt staan te) worden geïntroduceerd.

Gebruikte afkortingen:

BI:	BetrouwbaarheidsInterval
CLL:	Chronische Lymfatische Leukemie
DBC:	DiagnoseBehandelingCombinatie
ECR:	Eindhoven Cancer Registry (Eindhovense KankerRegistratie)
ENCR:	European Network of Cancer Registries (Europees Netwerk van KankerRegistraties)
EPM:	Eerdere Primaire Maligniteit
ICD-O-3:	International Classification of Diseases for Oncology, 3rd edition (Internationale Classificatie van Ziekten voor Oncologie, 3e editie)
IKNL:	Integraal Kankercentrum Nederland
IKZ:	Integraal Kankercentrum Zuid
KvL:	Kwaliteit van Leven
NKR:	Nederlandse KankerRegistratie
PHAROS:	Population-based HAematological Registry for Observational Studies
PROFILES:	Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (In het Nederlands PROFIEL genoemd)
SIR:	Standardised Incidence Ratio
SLL:	Small Lymphocytic Lymphoma (Kleincellig Lymfocytair Lymfoom)
WHO:	World Health Organization (Wereldgezondheidsorganisatie)

[4]) Voorbeelden van nieuwe therapieën zijn Obinutuzumab (in Europa geregistreerd in juli 2014), Idelalisib en Ibrutinib (registratie in Europa geadviseerd in juli 2014).

Dankwoord



Dankwoord

Dit boekje was nooit tot stand gekomen als ik niet omringd was door fijne mensen die allen op hun eigen wijze hieraan bijgedragen hebben. Ik wil hen hier dan ook graag bedanken.

Allereerst mijn promotoren; prof. dr. Coebergh en prof. dr. Van de Poll-Franse en copromotor dr. Posthuma:

Jan Willem, je onmetelijk grote kennis over kanker, statistiek, regelgeving, politiek, geschiedenis, geografie en waarschijnlijk 100.000 andere onderwerpen is imposant. Maar ik ben nog meer onder de indruk van de manier waarop jij me door het promotietraject hebt geleid. Met je niet te stuiten pogingen om mijn schrijfsels te perfectioneren, aanstekelijke geestdrift en oprechte interesse in mijn mormels vind ik je met recht een bijzonder hoogleraar. Bedankt voor je wijze lessen waar ik de rest van mijn leven wat aan zal hebben.

Lonneke, er is een moment geweest dat ik overwoog de handdoek in de ring te gooien. Dat jij toen aangaf een deel van begeleiding op je te nemen, gaf de doorslag om toch door te gaan. Jij beschikt over vele kwaliteiten en talenten, op zowel inhoudelijk als sociaal gebied. Het meest bijzondere vind ik dat je kritiek kan leveren op zo'n manier dat niet alleen de kwaliteit van mijn werk maar ook mijn zelfvertrouwen toenam. Bedankt voor een geweldig staaltje empowerment!

Ward, ik voelde me vaak ontzettend onnozel als het om hematologie ging, maar aan jou durfde ik alles te vragen, vertrouwend op je uitermate sympathieke karakter. Dankzij het inkijkje in de dagelijkse klinische praktijk dat je bood en de tijdige bijsturing waar nodig, voorkwam je dat ik de klinische relevantie van het onderzoek uit het oog verloor. Bedankt voor de tijd die je hebt genomen om me op dit vlak op een fijne manier te begeleiden.

Dit onderzoek was niet mogelijk geweest zonder de basis: het PHAROS-project. Ik wil de PHAROS-werkgemeenschap daarom bedanken voor dit mooie initiatief en de samenwerking. In het bijzonder veel dank voor Kees van Bezooijen. Door jou werd duidelijk dat de ijsberg zo veel groter is dan we dachten. Je energie en doorzettingsvermogen, en de manier waarop je deze gebruikte om je in te zetten voor patiëntenbelangen en onderzoek dat de patiënt daadwerkelijk dient, hebben een verpletterende indruk op me gemaakt.

Graag wil ik de leden van de leescommissie, Prof. dr. Hooijkaas, prof. dr. Van der Bom en prof. dr. Van Oers, bedanken voor de beoordeling van het proefschrift. Ook gaat mijn dank uit naar de overige leden van de promotiecommissie voor het zorgvuldig lezen van mijn proefschrift. Ik kijk uit naar de gedachtewisseling.

Co-auteurs Goda Choi, Olga Stam, Carel van Noesel, Sanne Tonino, Arnon Kater, Saskia van de Schans, Henrike Karim-Kos, Maryska Janssen-Heijnen, Wim Peters, Peet Nooijen, Lifang Liu, Isabelle Soerjomataram, Simone Oerlemans, Marten Nijziel, Volkher Scharnhorst, Ad Koster en Mirian Brink: bedankt voor jullie waardevolle bijdrage aan de artikelen en fijn dat alles in goede harmonie verliep.

Marlies, ik vrees dat ik één van de meest hysterische opdrachtgevers ooit was, met alle last-second aanpassingen. Bedankt voor je geduld en kalmte. Het is prachtig geworden.

Zonder data geen onderzoek. Ik ben de registratiemedewerkers van de NKR en PHAROS dankbaar voor hun niet aflatende inzet. In het bijzonder wil ik Anita de K., Anke, Anne-Marie, Boudewijn, Carolien, Marrigje, Sendy en Wil bedanken. Het was fijn dat jullie naast het registreren de tijd namen om me wegwijs te maken in de kunst van het registreren en met mee te denken over de aanpak. Ik heb veel gehad aan jullie ervaring en kennis.

Gitty en Erica, bedankt dat jullie altijd tijd maakten als ik weer eens een vraag over de NKR had, en daarnaast ook steeds een moment namen om te informeren hoe het met mij en mijn promotie ging.

Ook een deugdelijke applicatie om de data in te voeren en op te slaan was onmisbaar. Lucas, dank je wel voor de fantastische ondersteuning op alle vlakken. Dat het ongeveer twee jaar duurde voordat ik doorhad dat wij één van je vele klanten waren en je niet fulltime als gedetacheerde voor de NKR werkte, zegt genoeg.

Louis, de bereidheid om wat van jouw enorme kennis van SAS met mij te delen, gecombineerd met je geniale gevoel voor humor, maakte het voor mij nog lastiger om me tot het schrijven van artikelen in plaats van scripts te zetten. Bedankt voor je hulp bij het opzetten van het documentproject, de analyses en het relativeren van de drama's daaromheen.

Dr. Janny van den Eijnden, doordat ik enerzijds je enorme empathie naar je medewerkers en anderzijds je onverschrokken strijdlust voor je idealen van dichtbij heb mogen ervaren, ben je voor mij de meest memorabele directeur ooit. Bedankt voor het scheppen van een bijzonder prettig werkklimaat om in te promoveren.

De sfeer binnen de afdeling Onderzoek van het IKNL locatie Eindhoven is uniek. Of het nu ging om ondersteuning bij praktische problemen, een goed feestje bij leuke momenten of een bemoedigend woord bij tegenslagen, ik kon altijd en voor alles bij jullie terecht. Beste Liza, Saskia, Marieke, Valery, Mieke, Simone, Kim, Nicole H., Nicole E., Felice, Marjolein, Nienke, Melissa, Floor, Pauline, Erna, Michelle, Sandra, Anika en Corina; jullie maakten het fileleed dubbel en dwars de moeite waard!

Mijn paranimfen, van alle fijne collega's is de band met jullie extra bijzonder.
Rob, je hebt me zo vaak en uitgebreid geholpen met analyses, artikelen en aanverwante zaken, dat je bijna een tweede copromotor was.
Yvette, tegelijk met jou zwanger zijn, resulteerde (naast mooie kindjes uiteraard) in een fijne vriendschap. Ik hoop dat we in de toekomst nog veel bijkletsochtenden hebben!
Los van bovenstaande kan ik met jullie allebei gewoon geweldig goed lachen. Fijn dat jullie, na al die jaren waarin jullie me in lief en leed bijstonden, vandaag ook letterlijk bij me zullen staan.

Ook met mijn "nieuwe" collega's heb ik het getroffen. Hannelore, Bea, Jolanda, Lucy, Paul, Annette, Bert, Chantal, Caro en Ivette: bedankt voor de gezelligheid en het geduldig aanhoren van mijn promotie-perikelen.

Lieve vrienden en vriendinnen, hoewel ik zelf tijdens mijn promotietraject niet altijd even zichtbaar was als vriendin, realiseerde ik me des te meer hoe belangrijk jullie voor me zijn. Marieke van B., Marieke R., Heiny, Albertine, Cynthia, Neeltje, Lucy, Marloes, Sylvie, Martijn, Blanche, Thijs, Willem, Lenneke, Joost, Marijke, Alexander en Isabelle: Bedankt voor jullie interesse, begrip, steun en bovenal de broodnodige ontspanning.

Ook mijn fijne familie verdient het hier genoemd te worden. Oma, Björn, Ralph, Germaine, Richard, Mariska, Edwin, Hilary, Simon, Ryan, Jaydi, Britt, Gwenn en Casey: ik ben blij jullie in mijn leven te hebben. En da ge bedankt zèt, dè witte.

Anja, mijn bijzondere schoonloeder, jij verdient een aparte vermelding hier. Naast alle praktische hulp zoals op de kinderen passen, de tuin onder handen nemen en heerlijke maaltijden verzorgen, ben ik je ook dankbaar voor al die trappen onder mijn achterste. Je bood vanaf het prille begin van mijn relatie met Vincent altijd een luisterend oor als ik ergens mee zat, maar beëindigde dergelijke gesprekken steevast met de woorden "Als je je studie maar afmaakt!"

Lieve pap en mam, ook al was het niet altijd helder wat ik nu de hele dag uitspookte als "onderzoeker", jullie lieten altijd merken dat jullie trots waren op wat ik deed. Ook haalden jullie alles uit de kast om mij te ondersteunen. Dat begon ruim 15 jaar geleden toen jullie me door het hele land reden om open dagen van universiteiten te bezoeken. Het eindigde met de volledige overname van mijn huishouden. Bedankt voor alles.

Tot slot de allerbelangrijkste mensen in mijn leven:

Lieve Lis, dank je wel voor al die uren dat je me gezelschap hield als ik 's avonds laat achter de laptop zat, eerst vrolijk trappelend in mijn buik, later tevreden slapend op mijn borst in de draagzak. Zo werd de afronding van mijn proefschrift een stuk knusser.

Lieve Sten, bedankt voor al je fantastische verhalen en dolle acties waarmee je me altijd aan het lachen krijgt en alle dikke knuffels die me nog steeds doen smelten. Een betere manier om even te ontspannen bestaat er niet.

Voor jullie allebei:
Soms begin je in mijn hart te zingen
Waar het nacht was, heb jij lichtjes aangedaan
En door jou weet ik dan door te dringen
Tot de onvermoede schat van ons bestaan

Lieve Vincent, een promotietraject maakt het er niet altijd gezelliger op binnen een relatie. Maar ook deze ijsberg bleek geen partij voor ons huwelijksbootje, doordat jij onverzettelijk naast me bleef staan. Ik ben er dan ook van overtuigd dat we samen alle uitdagingen aankunnen die in de toekomst op ons pad komen.

Forever trusting who we are
And nothing else matters

Curriculum Vitae

Curriculum Vitae

Esther van den Broek werd op 13 maart 1981 in 's-Hertogenbosch geboren. In 1999 behaalde zij het VWO diploma aan het Ds. Pierson College in diezelfde stad, waarna zij startte met de studie Biomedische Gezondheidswetenschappen aan de Radboud Universiteit Nijmegen. Voor de afstudeerrichting pathobiologie werden twee stages verricht: een onderzoek naar de selectie van single-chain variable fragment antilichamen tegen ovariumtumor-gerelateerde glycosaminoglycanen met behulp van phage-display aan de afdeling Matrix Biochemie van het Nijmegen Centre for Molecular Life Sciences (Dr. van Kuppevelt) en een onderzoek naar de subcellulaire lokalisatie van het eiwit PRCC gedurende verschillende stadia van de celcyclus bij papillaire niercel-carcinomen met een t(X;1)(p11;q21) translocatie aan de afdeling Antropogenetica van het UMC St. Radboud te Nijmegen (Prof. Geurts van Kessel).

Na haar afstuderen in 2003 ging zij aan de slag als clinical datamanager bij Jansen-Cilag N.V. te Tilburg, om daar in 2007 de functie van Trial Centre Manager te vervullen.

Van 2009 tot 2014 was zij werkzaam bij het Integraal Kankercentrum Zuid te Eindhoven als junior-onderzoeker op het PHAROS-project. Hier hield zij zich bezig met het analyseren van kankerregistratiedata en SEER-data met betrekking tot CLL. Daarnaast leverde zij een bijdrage aan het opzetten van de dataverzameling en bijbehorende database in het kader van PHAROS-project voor wat betreft de CLL-gegevens en stuurde zij de gegevensverzameling aan.

In 2013 trad zij in dienst bij de stichting PALGA als adviseur landelijke zoekvragen. Hier coördineert zij gegevensaanvragen en voert deze uit. Tevens ontwikkelt zij voorstellen tot vernieuwing en uitbreiding van de dienstverlening en stimulering van wetenschappelijk onderzoek met gegevens uit de PALGA-databank.

List of publications

List of publications

Articles in this thesis

1. Choi G, van den Broek EC, Stam OCG, van Noesel CJM, Tonino SH, Kater AP. Increased incidence of T -cell malignancies in patients with chronic lymphocytic leukaemia. Submitted to Br J Haematol, 2014.
2. van den Broek EC, Kater AP, van de Schans SA, Karim-Kos HE, Janssen-Heijnen ML, Peters WG, et al. Chronic lymphocytic leukaemia in the Netherlands: trends in incidence, treatment and survival, 1989-2008. Eur J Cancer, 2011. 48(6): p. 889-95.
3. van den Broek EC, Liu L, Posthuma EF, Janssen-Heijnen ML, Coebergh JW, Soerjomataram I. Increased risk of chronic lymphocytic leukaemia among cancer survivors in the Netherlands: increased detection, causal factors or both? Ann Hematol, 2014. 93(1): p. 157-62.
4. van den Broek EC, Oerlemans S, Nijziel MR, Posthuma EF, Coebergh JW, van de Poll-Franse LV. Impact of active surveillance, chlorambucil, and other therapy on health-related quality of life in patients with CLL/SLL in the Netherlands. Ann Hematol, 2014.
5. van den Broek EC, Peters WG, Scharnhorst V, Koster A, Posthuma EFM, Coebergh JWW, et al. Underestimated time to treatment and survival rates due to underregistration of chronic lymphocytic leukemia in a population-based cancer registry. Submitted to Leuk Lymf, 2014.
6. van den Broek EC, Posthuma EFM, van de Poll-Franse LV, Brink M, Coebergh JWW, Maynadie M, et al. Towards optimal population-based registration of Chronic Lymphocytic Leukaemia. To be submitted, 2014.

Other articles

1. van Gestel YR, Rutten HJ, de Hingh IH, van den Broek E, Nieuwenhuijzen GA, Coebergh JW, et al. The standardised mortality ratio is unreliable for assessing quality of care in rectal cancer. Neth J Med, 2013. 71(4): p. 209-14.
2. Oerlemans S, Issa DE, van den Broek EC, Nijziel MR, Coebergh JW, Mols F, et al. Impact of therapy and disease-related symptoms on health-related quality of life in patients with follicular lymphoma: results of the population-based PHAROS-registry. Eur J Haematol, 2014.
3. Oerlemans S, Issa DE, van den Broek EC, Nijziel MR, Coebergh JW, Huijgens PC, et al. Health-related quality of life and persistent symptoms in relation to (R-)CHOP14, (R-)CHOP21, and other therapies among patients with diffuse large B-cell lymphoma: results of the population-based PHAROS-registry. Ann Hematol, 2014.

PHD PORTOFOLIO

Summary of PhD training and teaching activities

Name PhD student: *Esther van den Broek*
Erasmus MC Department: *Public Health / Netherlands Comprehensive Cancer Organisation*
PhD period: *2009-2014*
Promotors: *Jan Willem Coebergh & Lonneke van de Poll*
Supervisor: *Ward Posthuma*

	Year	Workload (Hours/ECTS)
Courses		
"Clinical epidemiology", Netherlands Institute for Health Sciences	2009	160 hours (5.7 ECTS)
"Cancer epidemiology", Netherlands Institute for Health Sciences	2010	40 hours (1.4 ECTS)
"Basiscursus oncologie", Nederlandse Vereniging van Oncology	2011	40 hours (1.4 ECTS)
Seminars and workshops		
Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen	2009	8 hours (0.3 ECTS)
"Subsidie aanvragen" & "Write it right" Nederlandse Organisatie voor Wetenschappelijk Onderzoek	2009	8 hours (0.3 ECTS)
"Leidinggeven voor beginners" & "Creatief denken" Nederlandse Organisatie voor Wetenschappelijk Onderzoek	2010	8 hours (0.3 ECTS)
Presentations		
Oral presentation PHAROS meeting	2009	8 hours (0.3 ECTS)
2x Oral presentation Tumour specific IKZ seminar	2009	64 hours (2.3 ETCS)
Oral presentation PHAROS meeting	2010	8 hours (0.3 ECTS)
Oral presentation Dutch hematology congress (DHC)	2010	32 hours (1.1 ECTS)
Oral presentation PHAROS meeting	2012	8 hours (0.3 ECTS)
Poster presentation European Cancer Congress (ECCO)	2013	32 hours (1.1 ECTS)
International conferences		
The Malignant B-Cell Symopsium , Uppsala University, Sweden	2009	8 hours (0.3 ECTS)
The European Cancer Congress (ECCO)	2013	16 hours (0.6 ECTS)
Dutch conferences		
Dutch Hematology Congress (DHC)	2009	16 hours (0.6 ECTS)
Werkgroep Epidemiologisch Onderzoek Nederland (WEON) conference	2010	16 hours (0.6 ECTS)
Eurocourse meeting	2010	16 hours (0.6 ECTS)
Werkgroep Epidemiologisch Onderzoek Nederland (WEON) conference	2011	16 hours (0.6 ECTS)
Teaching		
Training of registry clerks	2009-2012	160 hours (5.7 ECTS)

Conduction analyses and answering questions for medical specialists	2011	64 hours (2.3 ETCS)
Other		
Database design for PHAROS registry	2009-2012	160 hours (5.7 ECTS)
Total		**888 hours (31.8 ECTS)**