EUROPEAN JOURNAL OF CANCER 48 (2012) 889–895

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Chronic Lymphocytic Leukaemia in the Netherlands: Trends in incidence, treatment and survival, 1989–2008

E.C. van den Broek [a,*], A.P. Kater [b], S.A.M. van de Schans [a,c], H.E. Karim-Kos [d], M.L.G. Janssen-Heijnen [a,d], W.G. Peters [e], P.T.G.A. Nooijen [f], J.W.W. Coebergh [a,d], E.F.M. Posthuma [g]

[a] Dept. of Research, Comprehensive Cancer Centre South (IKZ), Eindhoven, The Netherlands
[b] Dept. of Haematology, Academic Medical Centre, Amsterdam, The Netherlands
[c] Dept. of Cancer Registry and Research, Comprehensive Cancer Centre the Netherlands, Nijmegen, The Netherlands
[d] Dept. of Public Health, Erasmus MC University Medical Centre Rotterdam, Rotterdam, The Netherlands
[e] Dept. of Internal Medicine, Catharina Hospital, Eindhoven, The Netherlands
[f] Dept. of Pathology, Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands
[g] Dept. of Internal Medicine, Reinier de Graaf Group, Delft, The Netherlands

ARTICLE INFO

Article history:
Available online 25 July 2011

Keywords:
Chronic Lymphocytic Leukaemia
Incidence
Survival
Epidemiology
Registries

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.

1. 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

* *Corresponding author:* Address: Comprehensive Cancer Centre South (IKZ), Eindhoven Cancer Registry, P.O. Box 231, 5600 AE Eindhoven, The Netherlands. Tel.: +31 40 2971616; fax: +31 40 2971610.
E-mail address: e.vd.broek@ikz.nl (E.C. van den Broek).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.06.053

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, randomised 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.

2. 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 6–12 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: 1st January 2010). Survival time was calculated as the time from diagnosis to death or to 1st 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 $\geqslant 75$ years). Incidence rates were also calculated for the populations 30–49 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 $y = \ln(\text{rate})$ and $x =$ calendar year, then $\text{EAPC} = 100 * (e^a - 1)$).

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 6 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.

3. 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).

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).

Table 1 – Age, sex and subclassification distribution of CLL patients in the Netherlands, 1989–2008.

	Males				Females			
	1989–1993 N (%)	1994–1998 N (%)	1999–2003 N (%)	2004–2009 N (%)	1989–1993 N (%)	1994–1998 N (%)	1999–2003 N (%)	2004–2009 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 (<1%)	0 (<1%)
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%)

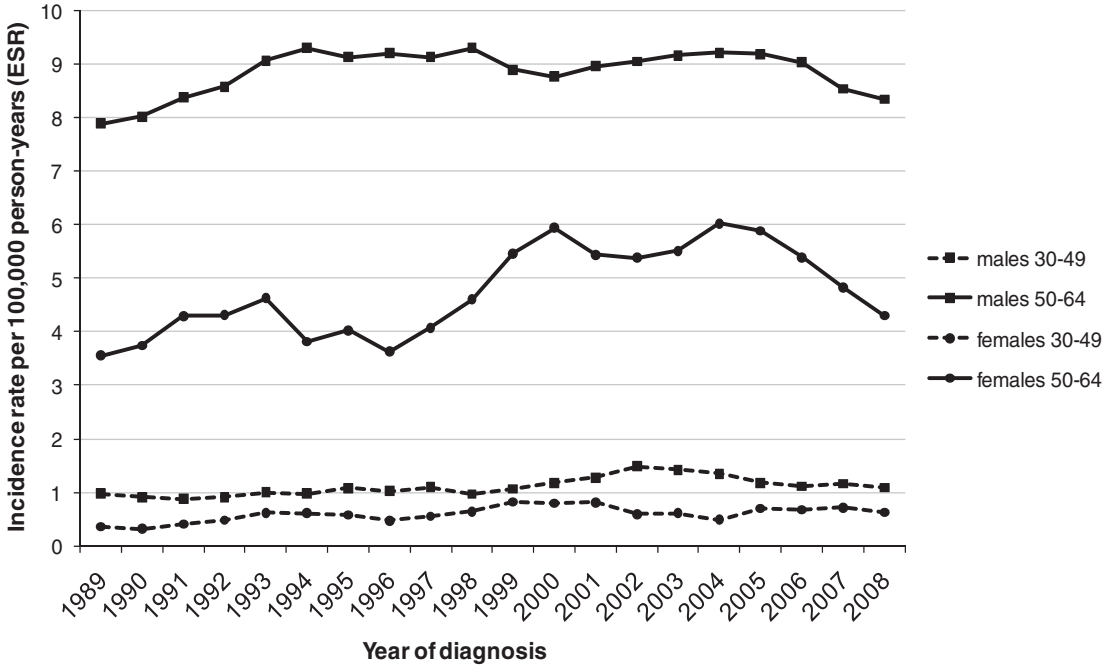

Fig. 1a – Three-year moving average of age-standardised incidence rates (ESR) of CLL in the Netherlands 1989–2008 according to gender, for patients aged 30–49 years and 50–64 years at diagnosis.

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 6 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 (Fig. 2).

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%, 10-year survival was stable around 45%. For females, one-year

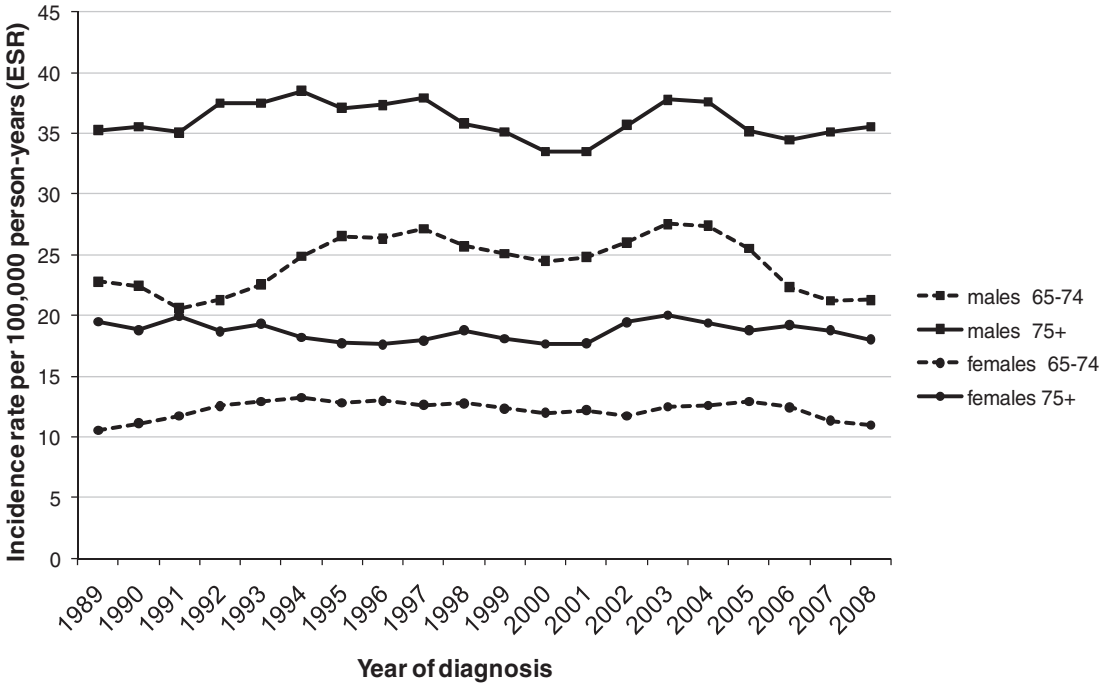

Fig. 1b – Three-year moving average of age-standardised incidence rates (ESR) of CLL in the Netherlands 1989–2008 according to gender, for patients aged 65–74 years and 75+ years at diagnosis.

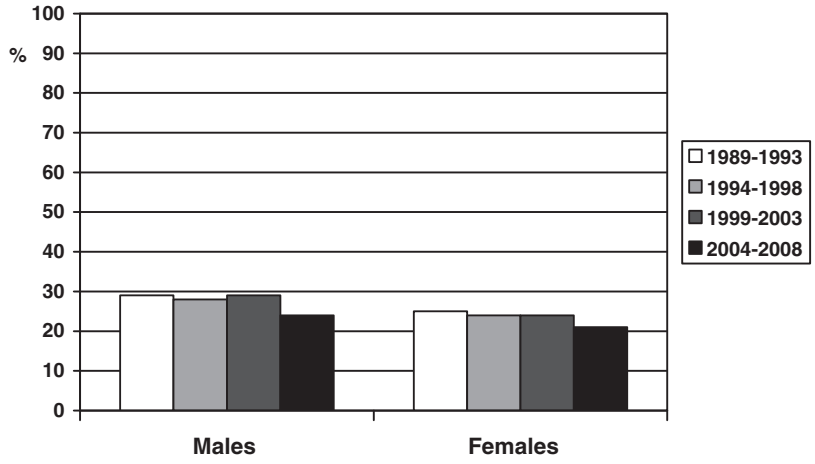

Fig. 2 – Proportion of patients treated with chemotherapy within 6 months of diagnosis, in the Netherlands, according to age, gender and period.

survival remained stable around 90%, three-year survival increased from 81% to 85%, five-year survival went from 71% to 76% and 10-year survival from 51% to 59%. Five- and 10-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).

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).

4. 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 6 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 to 2001 also reported a stable incidence rate.[15] In Denmark an increase in incidence

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

Age group	Survival rate after year	1989–1993	1994–1998	1999–2003	2004–2008
Males					
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					
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.

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 programme 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 and 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 an 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 that 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 6 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 towards the stronger in discouragement of treatment of indolent patients without active disease.[21–23] Another explanation is that diagnoses may have

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

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

* $P < 0.05$.

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.

Till 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.

Conflict of interest statement

None declared.

Acknowledgements

This study was performed as part of the project 'Progress against cancer in the Netherlands since the 1970s?' (Dutch Cancer Society Grant EMCR 2006-3489) and the PHAROS project (ZonMW Grant 152001007). The study sponsors had no role in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. We are grateful for the dedicated data collection by the various registration teams of the Netherlands Cancer Registry. The Output Committee of the Netherlands Cancer Registry provided and checked data from the various cancer registries (J. Flobbe, R. Damhuis, M. van der Heiden, P. Krijnen, K. Aben, L. van de Poll-Franse, S. Siesling, J. Verloop).

REFERENCES

1. http://seer.cancer.gov/.
2. Abrisqueta P, Pereira A, Rozman C, et al. Improving survival in patients with chronic lymphocytic leukemia (1980–2008): the Hospital Clinic of Barcelona experience. *Blood* 2009;**114**:2044–50.
3. Eichhorst B, Goede V, Hallek M. Treatment of elderly patients with chronic lymphocytic leukemia. *Leuk Lymphoma* 2009;**50**(2):171–8.
4. Brenner H, Gondos A, Pulte D. Trends in long-term survival of patients with chronic lymphocytic leukemia from the 1980s to the early 21st century. *Blood* 2008;**111**(10):4916–21.
5. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of chronic (mature) B and T lymphoid leukaemias. French-American-British (FAB) Cooperative Group. *J Clin Pathol* 1989;**42**(6):567–84.
6. Rawstron AC. Monoclonal B-cell lymphocytosis. *Hematol Am Soc Hematol Educ Program* 2009:430–9.
7. Ricci F, Tedeschi A, Morra E, Montillo M. Fludarabine in the treatment of chronic lymphocytic leukemia: a review. *Ther Clin Risk Manag* 2009;**5**(1):187–207.
8. Catovsky D, Richards S, Matutes E, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. *Lancet* 2007;**370**(9583):230–9.
9. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet* 2010;**376**(9747):1164–74.
10. www.ikcnet.nl.
11. Fritz A, Percy C, Jack A, et al. *International classification of diseases for oncology*. 3rd ed. Geneva: World Health Organisation; 2000.
12. Brenner H, Gefeller O, Hakulinen T. A computer program for period analysis of cancer patient survival. *Eur J Cancer* 2002;**38**(5):690–5.
13. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med* 2004;**23**(1):51–64.
14. Sant M, Allemani C, Tereanu C, et al. Incidence of hematological malignancies in Europe by morphological subtype: results of the HAEMACARE project. *Blood* 2010;**116**:3724–34.
15. Dores GM, Anderson WF, Curtis RE, et al. Chronic lymphocytic leukaemia and small lymphocytic lymphoma: overview of the descriptive epidemiology. *Br J Haematol* 2007;**139**(5):809–19.
16. Thygesen LC, Nielsen OJ, Johansen C. Trends in adult leukemia incidence and survival in Denmark, 1943–2003. *Cancer Causes Control* 2009;**20**(9):1671–80.
17. Otten JD, Broeders MJ, Fracheboud J, et al. Impressive time-related influence of the Dutch screening programme on breast cancer incidence and mortality, 1975–2006. *Int J Cancer* 2008;**123**(8):1929–34.
18. Bertakis KD, Azari R, Helms LJ, Callahan EJ, Robbins JA. Gender differences in the utilization of health care services. *J Fam Pract* 2000;**49**(2):147–52.
19. Cremers RG, Karim-Kos HE, Houterman S, et al. Prostate cancer: trends in incidence, survival and mortality in the Netherlands, 1989–2006. *Eur J Cancer* 2010;**46**(11):2077–87.
20. Molica S. Sex differences in incidence and outcome of chronic lymphocytic leukemia patients. *Leuk Lymphoma* 2006;**47**(8):1477–80.
21. Eichhorst B, Hallek M, Dreyling M. Chronic lymphocytic leukemia: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2008;**19**(Suppl.):ii60–=0?>ii62.
22. Eichhorst B, Hallek M, Dreyling M. Chronic lymphocytic leukemia: ESMO minimum clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009;**20**(Suppl.):102–4.
23. Cheson BD, Bennett JM, Grever M, et al. National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. *Blood* 1996;**87**(12):4990–7.
24. Kater AP, Tonino SH. Standards for the treatment of relapsed chronic lymphocytic leukemia: a case-based study. *Clin Lymphoma Myeloma Leuk* 2010;**10**(Suppl. 1):S34–41.
25. Kristinsson SY, Dickman PW, Wilson WH, et al. Improved survival in chronic lymphocytic leukemia in the past decade: a population-based study including 11,179 patients diagnosed between 1973–2003 in Sweden. *Haematologica* 2009;**94**(9):1259–65.
26. Shanafelt TD, Kay NE, Call TG, et al. MBL or CLL: which classification best categorizes the clinical course of patients with an absolute lymphocyte count $\geqslant 5 \times 10(9)$ L(−1) but a B-cell lymphocyte count $5 \times 10(9)$ L(−1)? *Leuk Res* 2008;**32**(9):1458–61.
27. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood* 2008;**111**(12):5446–56.
28. Zent CS, Kyasa MJ, Evans R, Schichman SA. Chronic lymphocytic leukemia incidence is substantially higher than estimated from tumor registry data. *Cancer* 2001;**92**(5):1325–30.
29. van de Schans SA, Issa DE, Visser O, et al. Diverging trends in incidence and mortality, and improved survival of non-Hodgkin's lymphoma, in the Netherlands, 1989–2007. *Ann Oncol* [Epub ahead of print].