

CHAPTER

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Chronic myeloid leukemia in the Netherlands: a population-based study on incidence, treatment and survival in 3,585 patients from 1989-2012

Submitted

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ABSTRACT

Most results on CML incidence, treatment and survival are derived from selected patients in clinical trials. To assess the impact and results of treatment of CML in the general population, we conducted a population-based, nation-wide study on 3,585 CML patients diagnosed between 1989 and 2012 in the Netherlands. Patients demographics were obtained from the National Cancer Registry. Information on age, gender, year of diagnosis, first treatment and date of death were recorded. Overall survival (OS) was adjusted for death rates in the normal population. Incidence in males decreased from 1.2 per 100.000 person years (PY) in 1989-2000 to 0.9 in 2001-2012. For females, incidence remained stable with 0.7 per 100.000 PY in both periods. Incidence was age dependent and highest in males in the last decades of life. Treatment before 2000 mainly consisted of chemotherapy, while after 2007 TKI use was 88%. Five-year relative survival was only 36% before the introduction of TKIs but significantly increased to 79% after the introduction of TKI. This study gives real-life insight in CML incidence, treatment and survival in the Netherlands. Although OS improved since the introduction of TKIs, there is still room for further improvement.

INTRODUCTION

Chronic myeloid leukemia (CML) is a chronic myeloproliferative disease, characterized by the presence of the Philadelphia chromosome, resulting from the (9;22) translocation coding for the BCR-ABL oncoprotein.^{1,2} Before the introduction of the tyrosine kinase inhibitors (TKIs) in 2001, allogeneic stem cell transplantation was the only curative treatment option. However, due to restrictions of age, performance score or donor availability, only a minority of CML patients could receive an allogeneic transplantation.^{3,4} In the others, only palliative improvement of disease outcome could be achieved with interferon, busulfan or hydroxycarbamide.⁵⁻⁷ Median time to transformation to accelerated phase and blast crisis was 3 to 5 years, with an inevitably fatal outcome.⁸ After the introduction of the first TKI imatinib in 2001, CML transformed from a highly fatal disease into a chronic illness with high response rates and good survival.^{9,10} In the 8-year follow up of the International Randomized Study of Interferon versus STI571 (IRIS study), 85% of patients were still alive.⁹ Following imatinib, other TKIs have been developed and introduced, among them nilotinib and dasatinib, with even higher response rates.^{11,12}

The efficacy of the different TKIs has been demonstrated in several company-sponsored studies. However, a drawback of these studies is that the results on treatment response and survival, as well as on demographic features, represent highly selected patients. Older or unfit patients, those with uncontrolled comorbidities or those who have non-typical CML related features, such as thrombocytopenia or extramedullary disease, were excluded from these trials.¹³⁻¹⁵ To give more insight in real-life epidemiology we retrospectively conducted a nation-wide population-based study on incidence, treatment and survival, on a large cohort of CML patients in the Netherlands. The aim of the study was to determine what the trends were in incidence, treatment and survival in all CML patients, regardless of enrollment in clinical trials.

METHODS

Data source and patients

All data were retrieved from the nationwide population-based Netherlands Cancer Registry (NCR), which aims to register all cancers in the Netherlands since 1989. The NCR collects data across all ages from all solid and hematological cancers, provides diagnostic and treatment criteria and monitors quality and facilitates collaborations.¹⁶ The NCR is primarily based on notifications from the national archive of histopathology and cytopathology (PALGA), where all pathological laboratories in the Netherlands are automatically reporting to. Besides, 5-10% of all cases (and up to one third of all leukemias) of the NCR are notified by the hospital discharge registries, hematological departments and, in recent years, from the medical claims departments. Medical charts of all cancer patients are studied by trained registrars, resulting in an accurate CML diagnosis after notification of a myeloproliferative neoplasm (MPN) by PALGA and/or the hospital discharge registry.

Diagnosis codes (topography and morphology) are registered according to the International Classification of Diseases for Oncology (ICD-O): the first edition of ICD-O (ICD-O-1) was used for cases diagnosed during 1989-1992, ICD-O-2 during 1993-2000 and ICD-O-3 since 2001.¹⁷⁻¹⁹

For this study, we selected all CML cases diagnosed during 1989-2012 with ICD-O morphology codes 9863/3 (chronic myeloid leukemia, not otherwise specified) and 9875/3 (chronic myelogenous leukemia, BCR-ABL positive). In the first and second edition of ICD-O BCR-ABL positivity was not a requisite to report a case as CML. Besides, specific codes for some other, BCR-ABL negative, myeloproliferative neoplasms (MPNs) were not available. Therefore, a number of these malignancies, amongst them atypical CML (aCML; morphology code 9876/3 introduced in ICD-O-3), chronic neutrophilic leukemia (CNL; morphology code 9963/3 introduced in ICD-O-3) and chronic myelomonocytic leukemia (CMML; morphology code 9868/3 introduced in ICD-O-2; 9945/3 in ICD-O-3), may have been classified as CML before 2001. All JMML cases (morphology code 9946/3 introduced in ICD-O-3) could be retrospectively removed from the study after medical chart revisions of all children with an unspecified chronic myeloid leukemia.

Basic information from the medical charts of all CML patients was collected, including date of birth, sex, postal code, date and hospital of diagnosis and primary treatment. Treatment in this study was categorized into four treatment groups as 'no therapy' (supportive care only), 'chemotherapy and/or interferon (IFN)' (including busulfan, hydroxycarbamide and cytarabine), 'hematopoietic stem cell transplantation' (HSCT, either autologous or allogeneic) and TKI. HSCT preceded by chemotherapy and/or IFN was categorized as HSCT. TKI in combination with chemotherapy and/or IFN and/or HSCT was categorized as TKI. Detailed data on the donor type of HSCT, second line treatments (including HSCT as a second line treatment) and response data are not available in the registry. Vital status of all Dutch residents is centrally registered and provided by the Dutch municipal registries. Vital status (death, alive or emigrated) for this study was complete until February 1st, 2014. Because from 2001 onwards a code for BCR-ABL positive CML was exclusively available in ICD-O-3 and, consequently, since 2001 no other MPNs were included in the selection for this study, and furthermore because the first TKI was introduced in 2001, we chose to separate the calendar periods in at least one or more before 2001 and from 2001 onwards.

Statistical analysis

Age and sex specific incidence rates were calculated using the number of residents provided by the Dutch municipal population registries. Age standardized incidence rates (ASR), using 5-year age groups and standardized according to the European standard population, were calculated per 100.000 person years (PY). Incidence rates were calculated using calendar periods 1989-1994, 1995-2000, 2001-2006 and 2007-2012.

Relative survival (RS) was calculated to assess CML survival. RS provides the excess mor-

tality associated with the diagnosis of CML, irrespective of the cause of death. RS was calculated from diagnosis until reported death, adjusted by the death rates in the general population, as calculated by Statistics Netherlands. Survival rates were compared by gender, by three calendar periods (1989-2000, 2001-2006 and 2007-2012) and by six age groups (0-17, 18-40, 41-60, 61-70, 71-80 and > 80 years old). Survival comparisons between groups were performed using 95% confidence intervals: in case there was no overlap in 95% confidence intervals, differences between groups were considered statistically significant. All analyses were performed with STATA version 13.

RESULTS

Incidence

Table 1 shows the patient demographics. A total of 3,585 patients were registered, 1,779 patients were diagnosed during period 1989-2000 and 1,806 during period 2001-2012. The median age was 65 years for patients diagnosed during 1989-2000 (males 64; females 67) and decreased to 59 years in 2001-2012 (males 58; females 61). Fifty-two percent of CML patients (1989-2000 57%; 2001-2012 48%) were over 60 years of age at diagnosis, while 33% (1989-2000 38%; 2001-2012 29%) were 70 years or older. Sixty one cases of CML were diagnosed in children up to the age of 17 (1.7% of all cases).

The ASR of CML remained stable during the study period (0.9 per 100,000 PY in 1989-2000 and 0.8 per 100,000 PY in 2001-2012) (Figure 1A). Incidence was higher in males than in females, but the male-to-female ratio decreased from 1.7 in 1989-2000 to 1.3 in 2001-2012. The decrease in the male-to-female-ratio was caused by a decrease in the ASR in males (1.2 and 0.9 in 1989-2000 and 2001-2012, respectively) and a stable ASR in females (0.7 both during 1989-2000 and 2001-2012). Figure 1B shows that up to the age of 65 rates for males and females are almost equal, but that there is a male predominance at higher ages. The highest age specific rates are observed in elderly patients. Age specific incidence rates in elderly males and females are lower between 2001-2012 compared to 1989-2000, with the largest difference in elderly males (Figure 1C). The age specific rates below the age of 60 are almost equal in 1989-2000 and 2001-2012, both in males and in females.

Treatment

Treatment data were unavailable for 28 patients who died at the date of diagnosis and 45 patients for which the files were not accessible, leaving 3,512 cases for the analysis of treatment. In the calendar period 1989-2000, treatment was recorded for 1,717 patients. Patients were given chemotherapy, including hydroxycarbamide (n = 942; 55%), a combination of chemotherapy and interferon (n = 159; 9%) or interferon single therapy (n = 26; 2%), 4 patients already received imatinib and 137 (8%) patients received an HSCT, all below the age of 61. Twenty-six percent (n = 449) of all CML patients did not receive any treatment. Eighty-six percent of them were older than 60 years.

Table 1. Distributions of patients over the different age groups and time periods

Age	Males				Age	Females			
	1989-2000		2001-2012			1989-2000		2001-2012	
	No.	%	No.	%		No.	%	No.	%
<18	17	2%	26	3%	<18	6	1%	12	1%
18-40	166	16%	182	19%	18-40	107	14%	115	14%
41-60	281	27%	325	33%	41-60	188	25%	282	34%
61-70	200	19%	188	19%	61-70	137	18%	157	19%
71-80	247	24%	185	19%	71-80	188	25%	157	19%
>80	122	12%	71	7%	>80	120	16%	106	13%
Total	1033		977		Total	746		829	

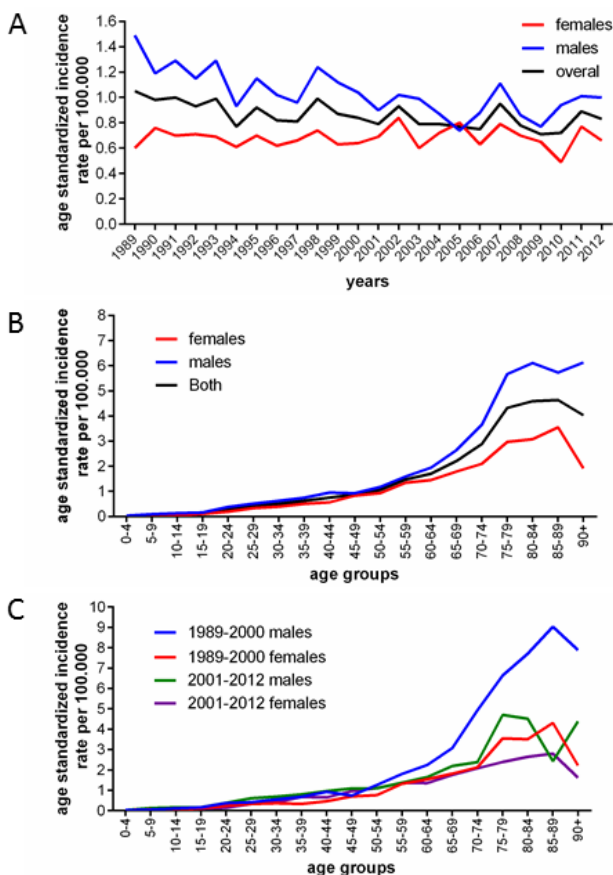


Figure 1. (A) Overall incidence and incidence in males and females per 100.000 person years per year throughout the study period. (B) incidence divided per age group and sex. (C) incidence by age group, sex and calendar period

For the period 2001-2006, data on treatment with TKI were only complete for 208 out of 874 patients (24%), because TKI use in this period was recorded in the same way as chemotherapy in most parts of the Netherlands. Fifty-four percent of patients ($n = 112$) was treated with a TKI, increasing from 18% in 2001 to 83% in 2006 while 30% ($n = 63$) was treated with chemotherapy (with or without interferon). During 2001-2006 34% of patients aged 61-70 years did not receive TKI treatment, while this proportion increased to 58% and 76% for patients aged 71-80 and above age 80, respectively. Out of all 874 patients 6% ($n = 49$) received an HSCT. Twelve percent of patients ($n = 103$) did not receive any therapy at all, from which 10% is under the age of 61.

During 2007-2012 ($n = 921$), wherein all CML patients undoubtedly had access to TKI therapy, TKI use has increased to 88% ($n = 809$). Six percent (59 patients) of patients were treated with chemotherapy or interferon and 1% ($n = 10$) received an HSCT. The percentage of TKI-naïve patients had thus decreased to 12% (9%, 20% and 41% in age groups 61-70, 71-80 and 80+ years, respectively). The percentage of patients not receiving any treatment had decreased to 5% ($n = 43$), all but one being over 60 years of age.

Figure 2 shows the treatment compositions during the different calendar periods.

Survival

RS rates for the different periods are shown in Figure 3. For the cohorts 1989-2000, 2001-2006 and 2007-2012, 5-year RS for all age groups together was 36% (95% CI 34-39%), 69% (95% CI 66-73%) and 79% (95% CI 75-83%), respectively. 10-year RS for the cohorts 1989-2000 and 2001-2006 were 25% (95% CI 22-27%) and 63% (95% CI 59-67%), respectively. For the cohort 2007-2012 10-year follow up is not reached yet. Five- and 10-year RS for the various age cohorts are shown in Table 2.

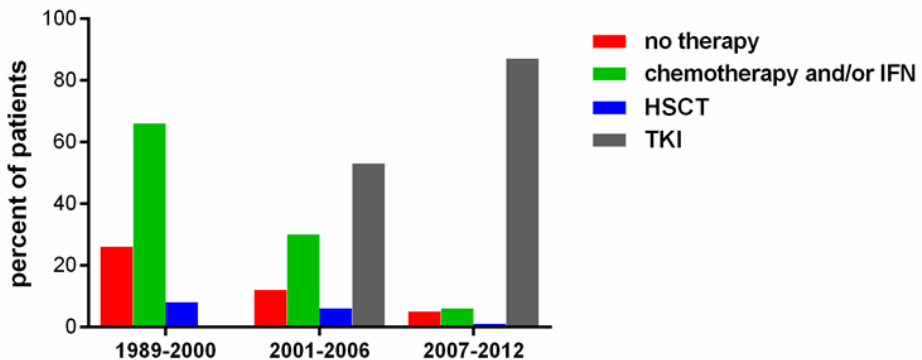


Figure 2. Distribution of the different treatment modalities during periods 1989-2000, 2001-2006 and 2007-2012. IFN = interferon

There were major differences in survival between the age cohorts, with the highest RS in the younger patients under 61 years of age, while the lowest RS was seen in the oldest of age (Figures 4A-C).

Next, we assessed the impact of the introduction of TKI therapy on overall survival. Figure 5 shows the change in the RS in 2001-2006 and 2007-2012, respectively, in comparison to 1989-2000. An improvement of the 5- and 10-year RS was observed for all age groups between calendar periods 1989-2000 and 2001-2006 (Figure 5A). Although this was statistically significant for most age groups, this did not apply to the 5- and 10-year RS for age group 0-17 and to the 5-year RS for patients aged > 80 years. Even a larger improvement in survival was seen in the time period 2007-2012 in comparison to 1989-2000 (Figure 5B). Five-year RS for all age groups combined increased with 43%, from 36% (95% CI 34%-39%) to 79% (95% CI 75%-83%). For patients younger than 17 years of age RS improved from 42% to 90% (+48%), for patients aged 18-40 from 59% to 90% (+31%), for patients aged 41-60 from 45% to 87% (+42%), for patients aged 61-70 from 35% to 86% (+51%), for patients aged 71-80 from 22% to 61% (+39%) and for patients older than 80 years from 12% to 34% (+22%) between first and last calendar period under study.

Finally, RS was not statistically significantly different between the two sexes, although the rates were slightly higher for women.

DISCUSSION

Population-based studies provide incidence rates and avoids bias in treatment and survival and give more accurate real-life statistics of diseases. Furthermore, they can provide insight in cost efficacy and help healthcare planning. In this study we collected nationwide unselected data from 3,587 CML patients over 24 years. This study provides important insight into the status of CML treatment and survival in the Netherlands. With 3,587 patients included, it is one of the largest studies on CML epidemiology ever performed.

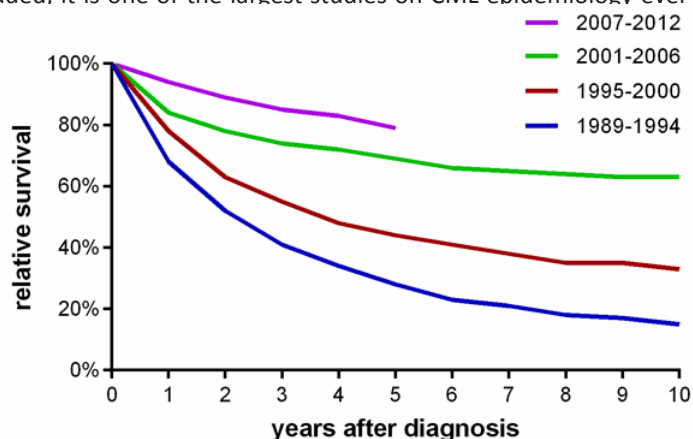


Figure 3. Relative survival rates for all ages in the different calendar periods

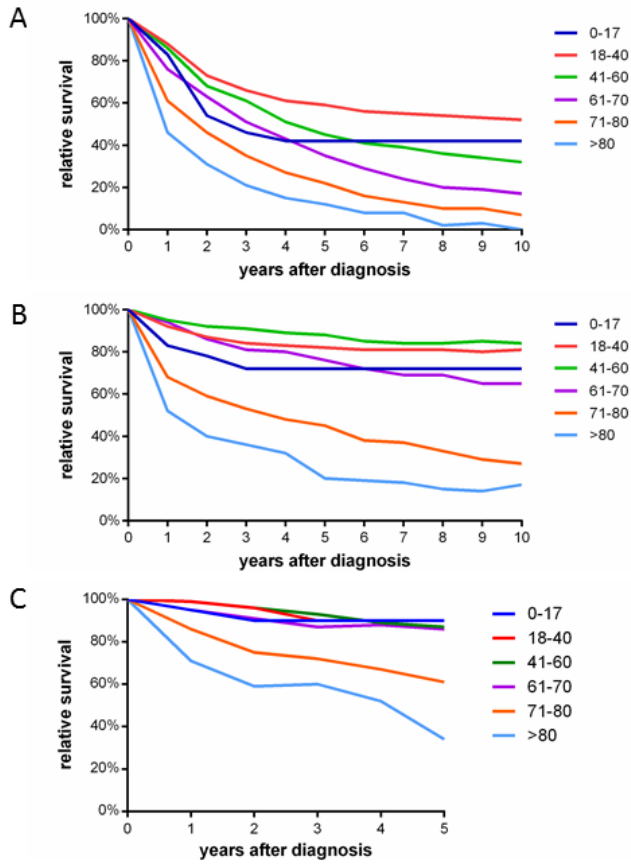


Figure 4. Relative survival rates for (A) cohort 2001-2012, (B) cohort 2001-2006 and (C) cohort 2007-2012

Table 2. 5- and 10 year relative survival rates of the different calendar periods an different age groups

Age	relative survival									
	1989-2000				2001-2006				2007-2012	
	5-yr (%)	95% CI (%)	10-yr (%)	95% CI (%)	5-yr (%)	95% CI (%)	10-yr (%)	95% CI (%)	5-yr (%)	95% CI (%)
all ages	36	34-39	25	22-27	69	66-73	63	59-67	79	75-83
0-17	42	22-60	42	22-60	72	46-87	72	46-88	90	65-97
18-40	59	53-65	52	46-58	82	74-88	81	72-87	90	83-94
41-60	45	40-50	32	28-37	88	83-91	84	78-89	87	81-91
61-70	35	29-41	17	12-22	76	67-83	65	55-75	86	77-93
71-80	22	17-27	7	4-12	45	36-54	27	17-39	61	48-73
> 80	12	6-19	0		20	11-33	17	5-41	34	17-55

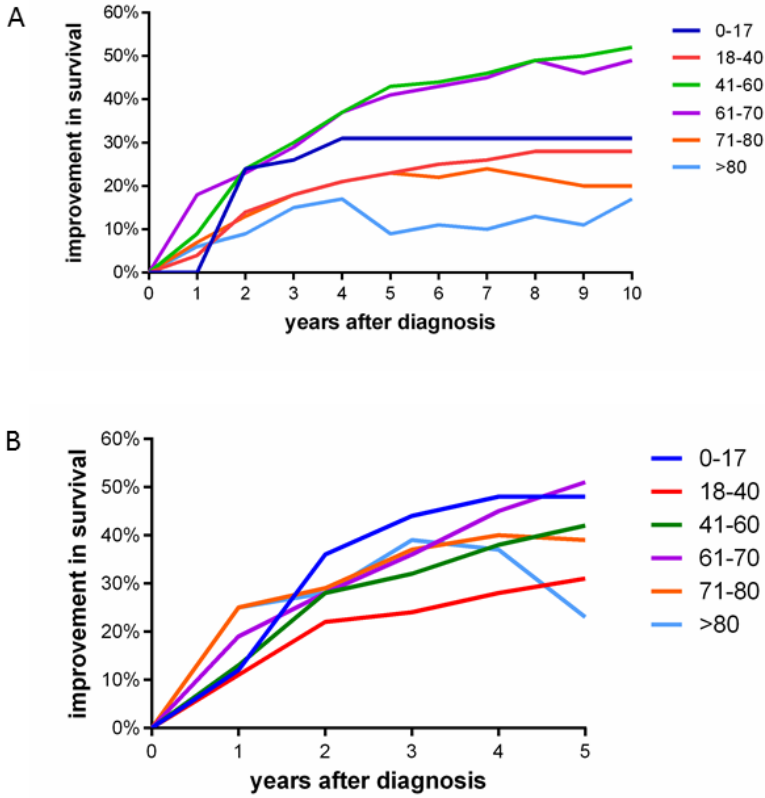


Figure 5. Improvement in relative survival for the different age groups between calendar periods (A) 2001-2006 and 1989-2000 and (B) 2007-2012 and 1989-2000

This is the first population-based study reporting on both incidence, treatment and survival of CML patients, focusing on narrow age groups, during a long period of 24 years and covering both the pre- and post TKI era.²⁰⁻³⁰ We found that the incidence of CML remained stable over time in both males and females. Incidence in the oldest of age was remarkably high, but decreased significantly over time. Incidence rates found in our study are lower than reported in the Surveillance, Epidemiology, and End Results program in the United States, who reported a remarkably high incidence of 1.75/100.000 but in line with population-based reports from Sweden, South-East-England, United Kingdom and Taiwan. Incidence rates in these studies varied between 0.72 to 1.2/100.000.^{21,22,26,27,29}

During the period 1989-2000 CML treatment mainly consisted of conventional chemotherapy, hydroxycarbamide or interferon. HSCT was restricted to patients under age 60 with good performance scores. Since 2001 the TKIs were prevalently used. We observed that after 2007, a time point at which all CML patients undoubtedly must have had access

to TKI therapy, still only 88% of patients were treated with any of the available TKIs. Most importantly, this implies that 12% were treated with other modalities or did not even receive any treatment at all. This is a substantial number considering the impact on survival of TKI therapy. Even more striking, almost half (44%) of patients ≥ 80 years old were not being treated with a TKI. This is much higher as reported in the Swedish population-based study, where 21% of patients above the age of 80 were not treated with a TKI between 2007 and 2009.²⁹

In the Netherlands, health insurance is compulsory for all citizens and imatinib, nilotinib and dasatinib are all reimbursed by the insurance companies as first line therapy, as well as for subsequent treatment lines. Therefore, there should be no financial hurdle to prescribe TKIs. The reason why some physicians do not treat CML patients upfront with a TKI remains speculative. There might be several reasons for this phenomenon. Firstly, CML patients might be treated by hematologists/oncologists or general trained internists in small practices with only very few CML patients. These physicians might be unfamiliar with the use of TKI therapy by lack of expertise and information. Secondly, as most patients not receiving TKI therapy are in the last decades of life, physicians might be cautious to prescribe a TKI to frail patients or patients with severe comorbidities because of unjustified fear for potential side effects.

Another interesting finding is that before 2001, only 8% of patients underwent an autologous or allogeneic stem cell transplantation as first line therapy. This percentage decreased to 6% in the early TKI period 2001-2006 and to 1% in the period 2007-2012 which corresponds to the Swedish population-based study where 5% of patients underwent an HSCT between 2002 and 2010²⁹, but is somewhat lower than reported in the Slovakian Camelia registry.²³ This finding reflects the reduced necessity for an allogeneic stem cell transplantation approach with the advent of TKIs.

The number of patients transplanted before 2001 is remarkable and lower than expected, and lower than the 20% reported in the Swedish population-based registry.²⁵

According to the NCR policy up to the beginning of the 1990s, only treatment information from the medical charts within 3 months after diagnosis was registered. HSCTs planned as first line therapy but performed beyond this 3 month period and not recognized by the registrars, were not registered. Therefore, we speculate that the number of transplants performed before the beginning of the 1990s is underreported in this study.

In this population-based study we observed significant survival gains for all ages after TKIs became available in the Netherlands. We expressly used RS to emphasize the impact of CML-related death. Five-year RS increased from 36% in the non-TKI period to 79% in the latest TKI calendar period. Considering the absolute increase in RS, patients aged 61-70 benefited most from the advances in treatment, while the oldest of age benefit fewest, although the 5-year RS more than doubled. Age still remains an important predictor of survival. There also was a significant difference in 5-year RS in calendar period 2001-2006

compared to 2007-2012 period. This further improvement in RS during the TKI era is probably due to broader incorporation of TKI use and the approval for usage of the second generation TKIs in 2006 (dasatinib) and 2007 (nilotinib) in the Netherlands. Despite the better RS rates, older patients, mainly those > 80 years old, still have low RS: 5-year RS for this age group is only 34%.

Not all RS rates can be accurately compared with other large population-based studies because of different calendar and age cohorts used. In the Swedish population-based study on 3,173 patients, the 5-year RS in diagnostic calendar periods 1994-2000 and 2001-2008 was 54% and 80% for all ages respectively²⁵, which is higher than in the resembling calendar periods 1995-2000 and 2001-2006 in our study (44% and 69% respectively). Furthermore, data from the Surveillance, Epidemiology, and END results (SEER) from the United States reported a 5-year RS of 36% for the pre-TKI calendar period 1990-2000 which is identical to the RS we observed in calendar period 1989-2000. On the contrary, 5-year relative survival rates in this study were clearly lower for 2001-2009 (56%) compared to the period 2001-2006 in our study (RS 69%).

It is evident that the progress in survival is a result of the availability of the first generation TKI imatinib since 2001. With imatinib therapy, most patients attain a complete cytogenetic response and progression to more advanced diseases substantially decreased to only 6% after 5 years.³¹ Second generation TKIs could be offered to resistant or intolerant patients as of 2006. In view of the further improvement in survival rates between 2001-2006 and 2007-2012, the availability of the second generation TKIs has resulted in even better outcome.³² Due to the progress in survival, CML prevalence is increasing. This has important financial consequences, since TKI treatment and also response monitoring is costly. This study has several limitations. Firstly, definitions of CML varied over time, and as a consequence, other, BCR-ABL negative, MPNs may have been registered as CML next to myeloid leukemia NOS in the first and second ICD-O editions. Several patients were reclassified retrospectively and all patients < 18 years old were revised with consequently no JMML bias. Nevertheless, we can not assure that our database contains some patients with aCML, CMML or CNL before 2001. To establish the potential bias in our data, we calculated the incidences of these MPNs from the NCR database according to the ICD-O-3 in the period 2001-2012. We observed that aCML and CNL are very rare diseases with mean annual incidences of 0.08 and 0.01/100.000 PY. Presuming that only a part of them were registered as CML, it is unlikely that they have influenced incidence and survival rates and treatment data significantly. For CMML, incidence is somewhat higher, 0.36/100.000 PY, and mainly affects males above 60 years of age (data not shown). Therefore, we assume that a major part of the higher CML incidence in elderly males during 1989-2000 in comparison to 2001-2012 is caused by misclassification of CMML as CML. Furthermore, a drawback of the NCR registry method is that we were not able to distinguish between autologous and allogeneic transplantation, as well as between the different chemothera-

peutic agents. To our knowledge, autologous HSCT was only performed in 19 patients included in the HOVON 39 trial.³³ However, on the whole, differentiating between conventional, intensive and TKI treatment is most important, which is provided by this study. Altogether, in spite of high TKI use and drastically improved survival for all age groups, survival rates in clinical studies are higher than in population-based studies.³⁴ For example, the 5-year follow up of the IRIS study showed that 89% of patients are still alive.³¹ For nilotinib and dasatinib 3-year OS is between 95% and 97%, which compares favorably with our results.^{11,12} This difference is attributed to selection of younger and healthier patients and better monitoring. It has been shown that centralization of CML care might be important to improve outcome.^{23,29} We argue that CML patients should be treated in specialized centers with good facilities for cytogenetic and molecular response monitoring and access to clinical studies, as well as supported by hematologists with CML expertise who are up to date regarding treatment and response guidelines, new drugs and decision making. In conclusion, in this population-based study on 3,587 CML patients with long-term follow and without selection bias, incidence slightly decreased during 1989-2000 but was stable after 2000 and increasing with age. With the advent of TKI therapy 5- and 10-year RS improved drastically. Although most patients were treated with a TKI after its introduction, some patients are still unjustly excluded from this effective therapy, which highlights the need for centralization of treatment in order to offer the best care for all CML patients. Moreover, although survival rates are getting better over time, there is still room for further improvement, especially in the elderly population.

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