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ORIGINAL REPORT

Success Story of Targeted Therapy in Chronic Myeloid Leukemia: A Population-Based Study of Patients Diagnosed in Sweden From 1973 to 2008

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
Chronic myeloid leukemia (CML) management changed dramatically with the development of imatinib mesylate (IM), the first tyrosine kinase inhibitor targeting the BCR-ABL1 oncoprotein. In Sweden, the drug was approved in November 2001. We report relative survival (RS) of patients with CML diagnosed during a 36-year period.

Patients and Methods
Using data from the population-based Swedish Cancer Registry and population life tables, we estimated RS for all patients diagnosed with CML from 1973 to 2008 (n = 3,173; 1,796 males and 1,377 females; median age, 62 years). Patients were categorized into five age groups and five calendar periods, the last being 2001 to 2008. Information on use of upfront IM was collected from the Swedish CML registry.

Results
Relative survival improved with each calendar period, with the greatest improvement between 1994-2000 and 2001-2008. Five-year cumulative relative survival ratios (95% CIs) were 0.21 (0.17 to 0.24) for patients diagnosed 1973-1979, 0.54 (0.50 to 0.58) for 1994-2000, and 0.80 (0.75 to 0.83) for 2001-2008. This improvement was confined to patients younger than 79 years of age. Five-year RSRs for patients diagnosed from 2001 to 2008 were 0.91 (95% CI, 0.85 to 0.94) and 0.25 (95% CI, 0.10 to 0.47) for patients younger than 50 and older than 79 years, respectively. Men had inferior outcome. Upfront overall use of IM increased from 40% (2002) to 84% (2006). Only 18% of patients older than 80 years of age received IM as first-line therapy.

Conclusion
This large population-based study shows a major improvement in outcome of patients with CML up to 79 years of age diagnosed from 2001 to 2008, mainly caused by an increasing use of IM. The elderly still have poorer outcome, partly because of a limited use of IM.

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INTRODUCTION

For too many years, chronic myeloid leukemia (CML) remained a leukemic subtype in which little or no improvement was gained with regard to overall survival. This was true despite numerous trials investigating radioactive phosphorous (P^{32}), splenic irradiation, splenectomy, single- or multiple-drug chemotherapy, and combined modality regimens. Eventually, a role for allogeneic bone marrow transplantation was explored, and this procedure became the treatment of choice for younger patients with an HLA-identical sibling donor. In addition, interferon alfa (IFN-α) therapy with or without cytarabine was included in the therapeutic arsenal.[1] The introduction of imatinib mesylate, the first tyrosine kinase inhibitor (TKI) specifically targeting the BCR-ABL1 oncoprotein, dramatically changed the strategy for patients in all phases of CML.[2] By taking advantage of high-quality population-based Swedish registries, we evaluated progress in outcome in relation to age, sex, and geographic region among 3,173 patients with CML diagnosed in Sweden between 1973 and 2008.

Our aim was to assess trends in patient survival and short- and long-term excess mortality among all patients, regardless of clinical trial enrollment, during this 36-year period. At the start of the study period, busulphan was the dominating therapeutic agent, followed by the more widespread use of

hydroxyurea and introduction of IFN-α and allogeneic stem-cell transplantation (SCT). Most importantly, imatinib mesylate was available in study protocols from 2000 and approved by authorities in November 2001.

PATIENTS AND METHODS

Central Registries and Study Population

Information regarding patients diagnosed with a malignant disorder in Sweden is reported to the population-based nationwide Swedish Cancer Registry, established in 1958. Every physician and pathologist/cytologist is obliged by law to report each occurrence of cancer to the registry. The Swedish Cancer Registry contains information on diagnosis, sex, date of birth, date of diagnosis, and hospital in which diagnosis was made, but it does not contain detailed clinical information such as symptoms, routine laboratory tests, treatment, or comorbidities.[3,4] All instances reported to the Swedish Cancer Registry are recorded using International Classification of Diseases Version 7. We identified all patients diagnosed with CML (code 205.1) between January 1, 1973, and December 31, 2008. Newly diagnosed patients in accelerated or blastic phase are included. The exact proportion is known for the period of 2002 to 2008 (Discussion).

Each resident in Sweden is given a unique national registration number used to index all health registries utilized in this study. For each individual, date of death is centrally registered in the nationwide Cause of Death Register. We obtained aggregate-level information on the total number of allogeneic and autologous SCTs performed in patients with CML in Sweden during the study period from the European Group for Blood and Marrow Transplantation Registry, established in 1974.

All patients were observed from date of diagnosis until death, emigration, or end of follow-up (December 31, 2009), whichever occurred first. The choice to include patients from 1973 was made based on the facts that by then, the Swedish Cancer Registry had reached a high rate of coverage[4-6] and that the first Swedish report on CML outcome included patients from that year.[7] We excluded individuals who had an emigration record before their first CML diagnosis and individuals diagnosed incidentally at autopsy. We did not exclude patients on the basis of previous cancer diagnoses. The Stockholm Ethical Review Board approved the study.

CML Treatment Principles During Study Period (1973-2008)

Busulphan was introduced in the treatment of CML in the mid 1950s and was the prevailing therapy in Sweden during the 1970s and early 1980s, leading to a median survival of 3.2 years.[7] However, the finding that inadvertent overdosage of busulphan could lead to irreversible marrow aplasia and possibly also early death in blastic transformation in comparison with hydroxyurea[8] led to an increasing use of the latter agent. Recommendations for management of patients with CML were introduced in 1984 by the Swedish CML Study Group, which was established the same year. Between 1984 and 1989, the Swedish CML Study Group randomly allocated approximately 35% of patients with newly diagnosed CML (n = 189) in Sweden to treatment with either hydroxyurea or busulphan.[9] No difference in overall or blast crisis–free survival was observed, although patients who underwent allogeneic SCT fared significantly better with a median survival of 4.7 years in comparison with 3.3 years in patients who did not undergo transplantation.[9] When it became clear that allogeneic SCT, despite a relatively high transplantation-related mortality, especially in the early years, could induce long-term Philadelphia chromosome negativity, it became the treatment of choice for eligible patients (Table 1). In patients younger than 55 years of age without a donor, the Swedish CML Study Group during the 1990s explored hydroxyurea and IFN-α[10] followed by one to three courses of intensive chemotherapy. Patients with significant Philadelphia chromosome reduction and negativity underwent high-dose therapy and autologous SCT to further minimize the Philadelphia-positive clone.[11,12] During the same period (1989-1997), the Swedish CML Study Group used an intensive chemotherapy protocol for patients in accelerated and blastic phase, including allogeneic or double autologous (ie, cells harvested in early chronic phase) SCT.[13] The advent of the novel molecularly targeted anticancer agent imatinib mesylate was a breakthrough in CML therapy.[2] In Sweden, clinical trials with imatinib mesylate started in December 2000, and the drug was approved for clinical use in November 2001. In total, 105 Swedish patients were included in four different clinical trials with imatinib mesylate from 2000 to 2001. Data from the Swedish CML Registry established in 2002 were used to identify prescription patterns of imatinib mesylate.[14,15]

Table 1. Demographic Characteristics of Patients Diagnosed With CML in Sweden From 1973 to 2008

Characteristic	Calendar Period										Total	
	1973 to 1979		1980 to 1986		1987 to 1993		1994 to 2000		2001 to 2008			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Total patients with CML	609	19.2	697	22.0	578	18.2	596	18.8	693	21.8	3,173	100
Age, years												
Median	62		66		64		59		59		62	
Range	2-93		1-94		2-96		1-95		0-99		0-99	
< 50	174	28.6	168	24.1	160	27.7	197	33.1	223	32.2	922	29.1
50-59	96	15.8	101	14.5	88	15.2	108	18.1	133	19.2	526	16.6
60-69	143	23.5	158	22.7	127	22.0	99	16.6	143	20.6	670	21.1
70-79	132	21.7	183	26.3	135	23.4	129	21.6	115	16.6	694	21.9
> 79	64	10.5	87	12.5	68	11.8	63	10.6	79	11.4	361	11.4
University hospital												
No	375	61.6	451	64.7	371	64.2	334	56.0	410	59.2	1,941	61.2
Yes	234	38.4	246	35.3	207	35.8	262	44.0	283	40.8	1,232	38.8
Sex												
Male	360	59.1	382	54.8	328	56.8	359	60.2	367	53.0	1,796	56.6
Female	249	40.9	315	45.2	250	43.2	237	39.8	326	47.0	1,377	43.4
Stem-cell transplantation												
Allogeneic	—	—	32	—	104	—	252	—	151	—	539	
Autologous	—	—	13		53		4		70			

Abbreviation: CML, chronic myeloid leukemia.

Survival Analysis

Relative survival ratios (RSRs) were computed as measures of CML survival.[16,17] The important advantage of using RS is that it does not rely on the accurate classification of cause of death. Instead, it provides a measure of total excess mortality associated with a diagnosis of CML, irrespective of whether the excess mortality is a direct or indirect result of the cancer. As such, the RSR captures excess mortality resulting from, for example, infection or second primary malignancies, which is not possible when using cause-specific survival. The RSR is defined as observed survival in the patient group (where all deaths are considered as events) divided by the expected survival of a comparable group from the general population, which is assumed to be free from the cancer in question. One-, 5-, and 10-year RSRs can be interpreted as the proportion of patients with CML who survived the malignancy at 1, 5, and 10 years, respectively. Expected survival was estimated using the Ederer II method[18] from Swedish population life tables stratified by age, sex, and calendar period. One-, 5-, and 10-year RSRs were calculated for patients diagnosed during five calendar periods (1973 to 1979, 1980 to 1986, 1987 to 1993, 1994 to 2000, and 2001 to 2008) and five age categories (< 50, 50 to 59, 60 to 69, 70 to 79, and > 79 years). Poisson regression was used to model excess mortality[19] to estimate the effects of the factors described while controlling for potential confounding factors. Parameter estimates from this model are interpreted as excess mortality rate ratios (EMRRs); an EMRR of 1.5, for example, for men/women indicates that men experience a 50% higher excess mortality rate (difference between observed and expected mortality) than women. All calculations were performed using Stata 11 (StataCorp, College Station, TX).

RESULTS

A total of 3,173 patients with CML, including 1,796 males (57%) and 1,377 females (43%) with a median age of 62 years (range, 0 to 99 years) diagnosed from January 1, 1973, to December 31, 2008, were included in the study (Table 1). Seventy patients (2.2%) were 18 years of age or younger. Thirty-nine percent of patients were diagnosed at university hospitals. Throughout the study period, there was a consistent male predominance (Table 1). There were no SCTs performed in patients with CML in Sweden before 1980. A total of 609 SCTs were reported to the European Group for Blood and Marrow Transplantation Registry from 1980 to 2008 (70 autologous and 539 allogeneic). Use of allogeneic SCT reached a peak in the calendar period of 1994 to 2000 (n = 252).

As shown in Figure 1, cumulative RS improved significantly with each calendar period during the study period, with greatest survival among patients diagnosed during the last calendar period (2001-2008). Five-year RSRs were 0.21 (95% CI, 0.17 to 0.24), 0.23 (95% CI, 0.20 to 0.27), 0.37 (95% CI, 0.33 to 0.41), 0.54 (95% CI, 0.50 to 0.58), and 0.80 (95% CI, 0.75 to 0.83) in the calendar periods 1973 to 1979, 1980 to 1986, 1987 to 1993, 1994 to 2000, and 2001 to 2008, respectively (Fig 1). Throughout all calendar periods, age was a strong predictor of survival, with superior survival for the youngest patients (Table 2; Fig 2). In analyses including age and period of diagnosis, RS clearly improved with calendar period in all age groups, but this was most pronounced in patients younger than 79 years of age, particularly those 70 to 79 years of age (Fig 2). Survival among all age groups was greatest during the last calendar period.

One-, 5-, and 10-year RSRs are shown in relation to age category and calendar period in Figure 3. Five-year RS for patients younger than 50 years of age improved from 0.26 (95% CI, 0.20 to 0.33) to 0.91 (95% CI, 0.85 to 0.94), for patients 70 to 79 years of age from 0.11 (95% CI, 0.06 to 0.19) to 0.75 (95% CI, 0.61 to 0.86), and for patients older than 79 years of age from 0.00 to 0.25 (95% CI, 0.10 to 0.47) between first and last calendar periods under study (Table 3; Fig 3).

Table 2 shows crude and adjusted EMRRs. When analyzing crude EMRR, year of diagnosis was significantly associated with survival. Estimated EMRRs were 0.33 (95% CI, 0.25 to 0.43) for the period of 2001 to 2008 and 3.14 (95% CI, 2.69 to 3.66) for the period of 1973 to 1979 compared with that of patients diagnosed from 1994 to 2000 (1.00; reference). In the adjusted EMRR analysis, similar results

Table 2. Crude and Adjusted EMRRs for 3,173 Patients With CML Diagnosed in Sweden From 1973 to 2008

Characteristic	EMRR*	95% CI	Adjusted EMRR†	95% CI
Time since diagnosis, years				
0-1	1.00	Reference	1.00	Reference
1-2	0.84	0.74 to 0.97	0.91	0.80 to 1.03
2-4	0.67	0.59 to 0.76	0.82	0.73 to 0.93
3-6	0.62	0.53 to 0.72	0.87	0.75 to 1.01
6-8	0.45	0.37 to 0.55	0.71	0.58 to 0.87
8-10	0.38	0.29 to 0.50	0.61	0.47 to 0.80
Year of diagnosis				
1973-1979	3.14	2.69 to 3.66	2.98	2.58 to 3.45
1980-1986	2.77	2.37 to 3.22	2.40	2.08 to 2.77
1987-1993	1.82	1.55 to 2.14	1.71	1.47 to 2.00
1994-2000	1.00	Reference	1.00	Reference
2001-2008	0.33	0.25 to 0.43	0.37	0.29 to 0.47
Age at diagnosis, years				
< 50	0.52	0.46 to 0.60	0.54	0.47 to 0.61
50-59	0.68	0.59 to 0.79	0.74	0.64 to 0.85
60-69	1.00	Reference	1.00	Reference
70-79	1.41	1.23 to 1.61	1.44	1.26 to 1.64
> 79	2.76	2.35 to 3.25	2.90	2.46 to 3.42
Sex				
Male	1.00	Reference	1.00	Reference
Female	0.94	0.85 to 1.03	0.84	0.76 to 0.92
University hospital				
No	1.00	Reference	1.00	Reference
Yes	0.79	0.72 to 0.87	1.02	0.93 to 1.13

Abbreviations: CML, chronic myeloid leukemia; EMRR, excess mortality rate ratio.
*Estimated from models including each covariate one at a time, adjusting only for follow-up time.
†Adjusted for all covariates simultaneously.

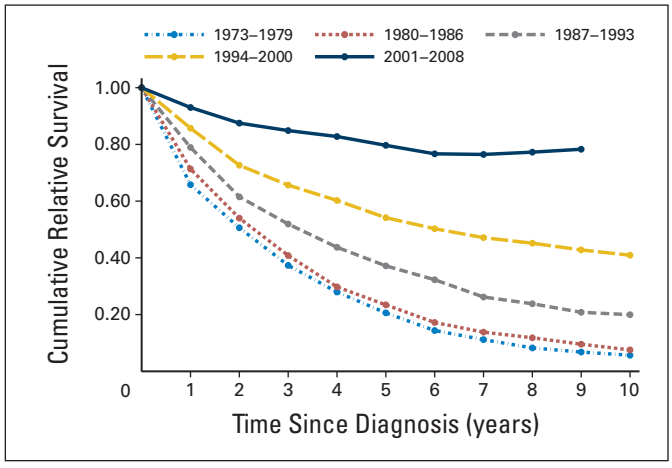

Fig 1. Relative survival ratios by calendar period of diagnosis.

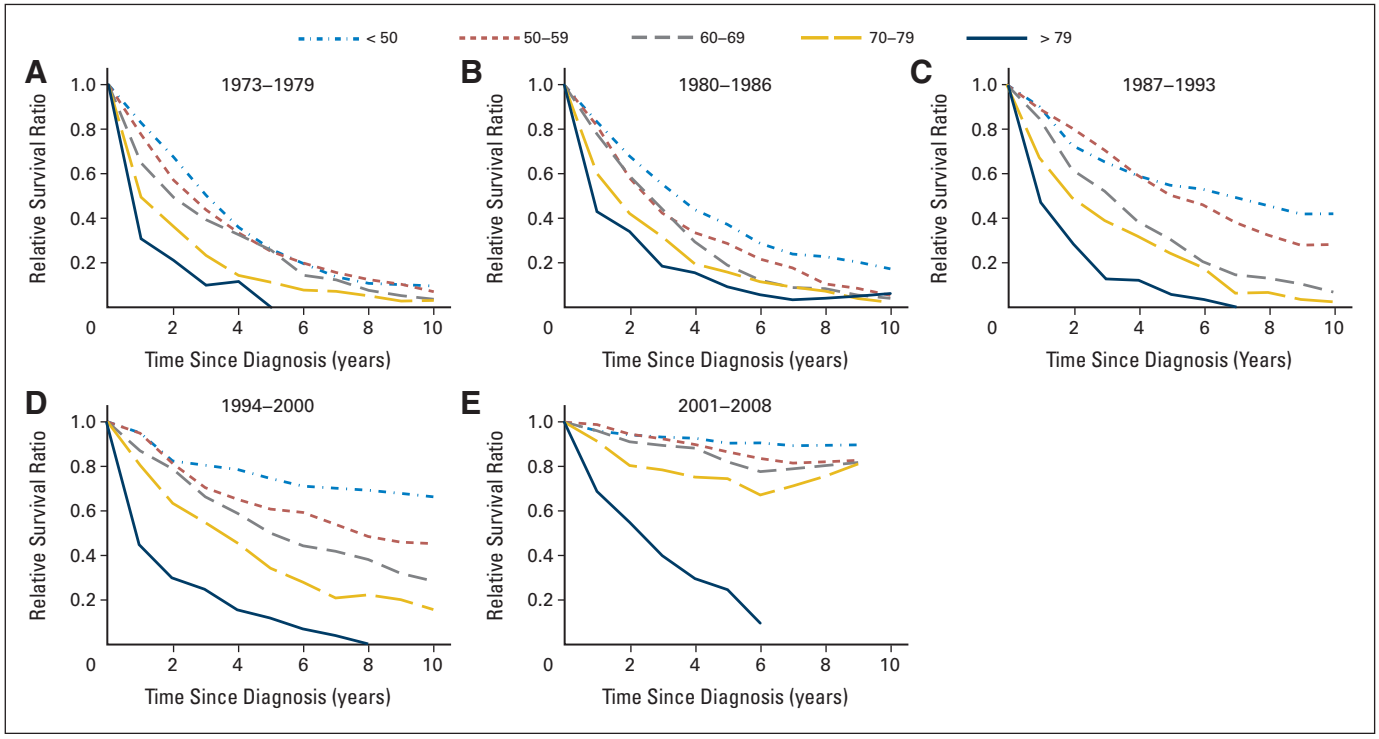

Fig 2. Cumulative relative survival by age (years) and period of diagnosis.

were seen (Table 2). Younger age at time of diagnosis was associated with a significantly lower excess mortality. For patients younger than 50 years of age at diagnosis, the adjusted EMRR was 0.54 (95% CI, 0.47 to 0.61), and for patients older than 79 years of age, it was 2.90 (95% CI, 2.46 to 3.42), compared with that for patients between the ages of 60 and 69 years (1.00; reference; Table 2). Females had a significantly better prognosis than males (EMRR, 0.84; 95% CI, 0.76 to 0.92) after adjusting for the remaining covariates (Table 2). There was a significant difference in crude EMRR between patients diagnosed at university compared with nonuniversity hospitals; however, the adjusted EMRR did not show any difference in outcome.

Data from the national CML registry revealed that imatinib mesylate was first-line treatment in 40%, 78%, and 84% of patents in the years 2002, 2004, and 2006, respectively. When analyzing first-line treatment in relation to age, we noticed that only 18% of patients older than 80 years of age received imatinib mesylate as upfront therapy, the large majority instead being treated with hydroxyurea.

DISCUSSION

We observed a significant improvement in survival starting in the 1987 to 1993 calendar period. Several factors probably contributed to the observed improvement in RS in the third calendar period under study. These include an increasing number of performed allogeneic SCTs, the introduction of IFN-α, and better supportive care. Whether more aggressive chemotherapy in both chronic and accelerated/blastic phases has contributed as well may be debated.[11,13] Most probably, these changes in the management of patients with CML affected the gradual improvement in survival, which was also manifested from 1994 to 2000, being most pronounced in patients younger than 60 years of age. Moreover, imatinib mesylate contributed to better outcome in patients diagnosed during this calendar period.

The most remarkable improvement in survival was observed in the last calendar period in patients younger than 79 years of age and was most pronounced in patients age 70 to 79 years. This dramatic change in outcome was certainly caused by an increasing use of mainly imatinib mesylate. Data from the national CML registry showed that imatinib mesylate was first-line treatment in more than 80% of patients in 2006.[14,15] However, a large majority of patients older than 80 years of age received hydroxyurea as upfront therapy, with only 18% being treated with imatinib mesylate. This likely explains the lack of significant survival improvement in this age category. Whether the low prescription of the drug was caused by economic or potential toxicity considerations or a combination of both remains unknown. Because second-generation TKIs were approved in 2007 (dasatinib) and 2008 (nilotinib), their impact on survival must have been limited in the present analysis. In the IRIS (International Randomized Study of Interferon Versus STI571) study, 6-year overall survival was 88%.[20,21] However, it should be noted that in a large single-institution study, 25% of patients had discontinued imatinib mesylate treatment because of unsatisfactory response and/or toxicity reasons by 5 years.[22] Notwithstanding, 5-year overall survival was 83.2%. It is thus gratifying to observe an overall RSR of 0.8 at 5 years in a population-based setting including not only patients in chronic phase at diagnosis. Thus, through the rather newly established (in 2002) Swedish CML Registry, we know that during the period of 2002 to 2008, 4% and 3% of patients presented in accelerated and blastic phases, respectively.[14,15] Unfortunately, this information is lacking for earlier calendar periods.

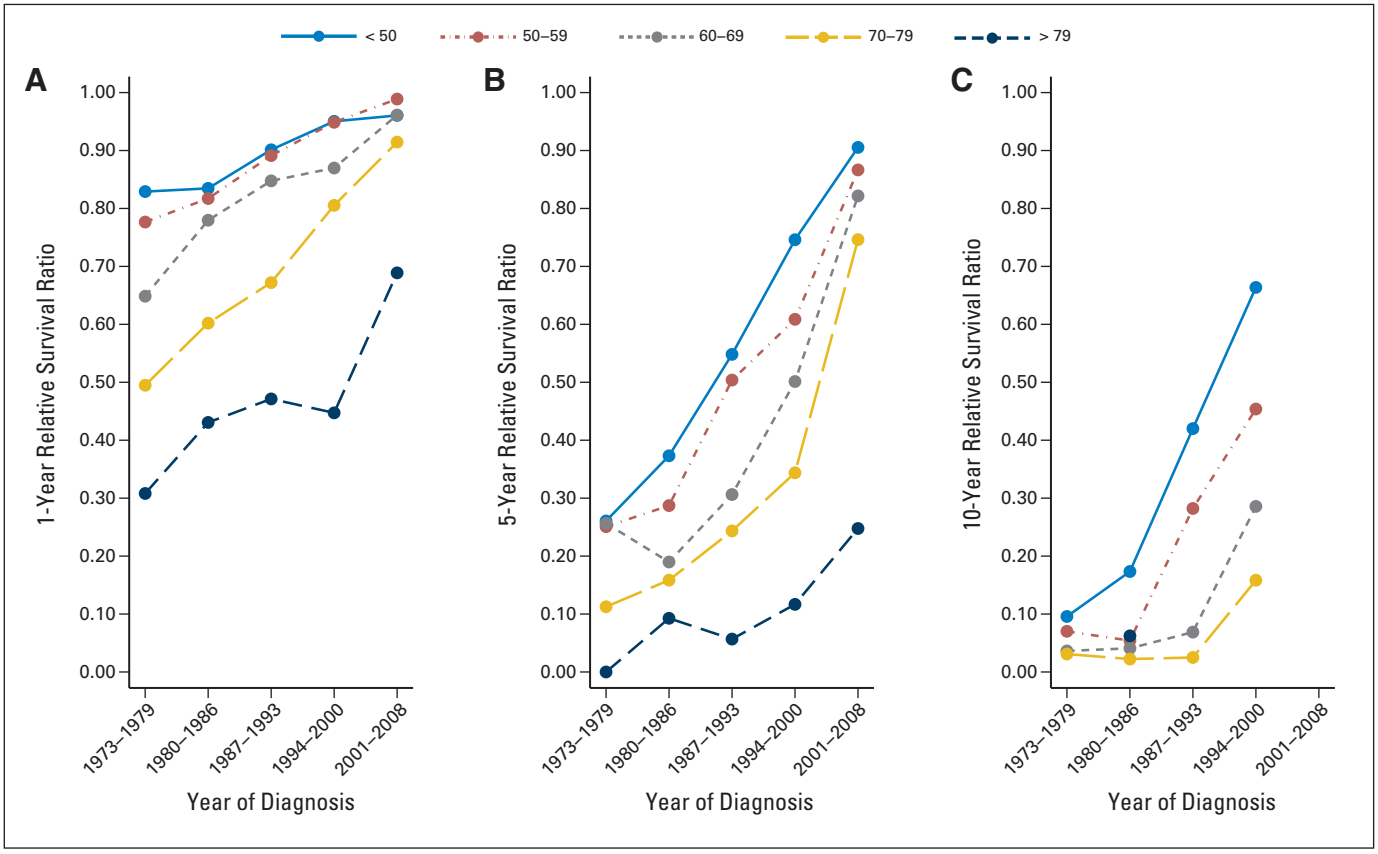

Fig 3. Estimates of 1-, 5-, and 10-year relative survival among patients with chronic myeloid leukemia in Sweden, stratified by age category and calendar period of diagnosis.

It should be noted that during the last 8-year period, the number of autologous and allogeneic SCTs decreased by 90% and 40%, respectively, in comparison with the preceding period. During 2002 to 2006, 5.9% of newly diagnosed patients (median age, 44 years; range, 25 to 63 years) underwent allogeneic SCT within 1 year of diagnosis. The present indications for allogeneic SCT in Sweden are in good accordance with the recommendations of European LeukemiaNet.[23]

Age remained an important predictor of survival during each individual calendar period. We also observed a moderately but statistically significantly better survival for women, when adjusting for age and calendar period. We made similar observations in large population-based studies in multiple myeloma, acute myeloid leukemia, and chronic lymphocytic leukemia.[24-26] The mechanisms underlying this sex-related difference in outcome are largely unknown.

There are few population-based studies on survival in CML, and most survival data are derived from clinical trials, which are associated with various degrees of patient selection. Brenner et al[27] performed a period analysis using SEER (Surveillance, Epidemiology and End Results) data. These authors restricted their analysis to estimating trends in relative survival among patients with CML from 1990 to 1992 and 2002 to 2004. In contrast with the present study, they did not find any statistically significant improvement of survival in patients 65 to 74 and 75 or more years of age. This probably reflects a less widespread use of imatinib mesylate in those age categories early after the introduction of the drug. Unfortunately, no information on use of TKIs was provided in that report. It should also be noted that our study, in contrast with that of Brenner et al, used a cohort approach. Cohort estimates represent the actual survival experience of a well-defined cohort of patients, which is not the case for period estimates.

Several factors support the robustness of our data. Swedish patients with CML are almost exclusively diagnosed and treated by physicians in nonprivate hospital-based hematology units, in good compliance with the national guidelines for CML. Furthermore, Sweden has a well-established government-funded public health care system, in which all residents by law are entitled to equal access to health services. As a consequence, treatment decisions are determined based on patient- and disease-related factors and should essentially be independent of financial considerations.

Limitations include lack of clinical data for individual patients (1973 to 2001). During the first calendar period, patients with Philadelphia chromosome–negative myeloproliferative disorders may erroneously have been reported as having CML to the cancer registry.[7] In addition, we do not have information regarding the proportion of patients whose disease was detected early in an asymptomatic state (lead-time bias) during the study period. However, early detection and therapy of asymptomatic CML may only marginally have affected the results. There is also a lack of information on potential confounders such as socioeconomic factors, smoking habits, and so on. However, the study design ensured adjustment for sex, age, and geography.

To conclude, in this large population-based study including more than 3,000 patients with CML, survival increased significantly after 2001 for patients up to 79 years of age. Future population-based studies will define the impact of second-generation TKIs on outcome

Table 3. Estimates of 1-, 5-, and 10-Year RS Among Patients With CML in Sweden Stratified by Age and Calendar Period of Diagnosis

	1 Year									
	1973-1979		1980-1986		1987-1993		1994-2000		2001-2008	
Age (years)	RS	95% CI	RS	95% CI	RS	95% CI	RS	95% CI	RS	95% CI
< 50	0.83	0.76 to 0.88	0.83	0.77 to 0.88	0.90	0.84 to 0.94	0.95	0.91 to 0.97	0.96	0.92 to 0.98
50-59	0.78	0.68 to 0.85	0.82	0.73 to 0.88	0.89	0.80 to 0.94	0.95	0.88 to 0.98	0.99	0.95 to 1.00
60-69	0.65	0.56 to 0.72	0.78	0.70 to 0.84	0.85	0.77 to 0.90	0.87	0.78 to 0.93	0.96	0.91 to 0.99
70-79	0.49	0.40 to 0.58	0.60	0.52 to 0.67	0.67	0.58 to 0.75	0.81	0.72 to 0.87	0.92	0.84 to 0.96
> 79	0.31	0.19 to 0.44	0.43	0.32 to 0.54	0.47	0.34 to 0.60	0.45	0.31 to 0.58	0.69	0.56 to 0.80
	5 Years									
	1973-1979		1980-1986		1987-1993		1994-2000		2001-2008	
	RS	95% CI	RS	95% CI	RS	95% CI	RS	95% CI	RS	95% CI
< 50	0.26	0.20 to 0.33	0.37	0.30 to 0.45	0.55	0.47 to 0.62	0.75	0.68 to 0.80	0.91	0.85 to 0.94
50-59	0.25	0.17 to 0.34	0.29	0.20 to 0.38	0.50	0.39 to 0.61	0.61	0.51 to 0.70	0.87	0.78 to 0.92
60-69	0.26	0.18 to 0.34	0.19	0.13 to 0.26	0.31	0.22 to 0.39	0.50	0.39 to 0.60	0.82	0.72 to 0.90
70-79	0.11	0.06 to 0.19	0.16	0.10 to 0.23	0.24	0.17 to 0.33	0.34	0.25 to 0.44	0.75	0.61 to 0.86
> 79	0.00		0.09	0.03 to 0.21	0.06	0.01 to 0.18	0.12	0.04 to 0.26	0.25	0.10to 0.47
	10 Years									
	1973-1979		1980-1986		1987-1993		1994-2000		2001-2008	
	RS	95% CI	RS	95% CI	RS	95% CI	RS	95% CI	RS	95% CI
< 50	0.10	0.06 to 0.15	0.17	0.12 to 0.24	0.42	0.34 to 0.50	0.66	0.59 to 0.73	—	
50-59	0.07	0.03 to 0.14	0.05	0.02 to 0.11	0.28	0.19 to 0.38	0.45	0.35 to 0.55	—	
60-69	0.04	0.01 to 0.08	0.04	0.02 to 0.09	0.07	0.03 to 0.13	0.29	0.19 to 0.39	—	
70-79	0.03	0.01 to 0.10	0.02	0.01 to 0.07	0.03	0.01 to 0.08	0.16	0.08 to 0.26	—	
> 79	0.00		0.06	0.01 to 0.30	0.00		0.00		—	

Abbreviations: CML, chronic myeloid leukemia; RS, relative survival.

and also whether increased use of TKIs among elderly patients will improve prognosis in this age category.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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