Recent trends in long-term survival of patients with chronic myelocytic leukemia: disclosing the impact of advances in therapy on the population level

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ABSTRACT

Within the past decades, major advances in therapy for chronic myelocytic leukemia, including allogeneic hematopoietic stem cell transplantation, interferon therapy, and, more recently, also therapy with the tyrosine kinase inhibitor imatinib, have entered clinical practice. The impact of these advances on long-term survival on the population level should be disclosed as timely as possible. We estimated trends in age specific 5- and 10-year relative survival of chronic myelocytic leukemia patients in the United States from 1990-1992 to 2002-2004. Our analysis is based on records from 8,329 patients aged 15 years or older with a first diagnosis of chronic myelocytic leukemia included in the 1973-2004 data base of the Surveillance, Epidemiology, and End Results Program. Period analysis was used to disclose recent developments with minimum delay. Overall, 5-year relative survival increased from 27 to 49%, and 10-year relative survival increased from 9.5 to 34% between 1990-92 and 2002-04. The increase was most dramatic for younger patients, with 10-year relative survival increasing from 16 to 72% in age group 15-44 years, from 12 to 54% in age group 45-54 years, and from 8 to 34% in age group 55-64 years ($p<0.0001$ in all cases). Improvements were more modest and not statistically significant, and survival remained at much lower levels among age groups 65-74 and 75+ years. Our analysis discloses a dramatic recent increase in long-term survival of younger patients with chronic myelocytic leukemia which most likely reflects rapid dissemination of advances in therapy on the population level.

Key words: cancer registries, chronic myelocytic leukemia, survival, therapy.

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Introduction

Major breakthroughs in clinical research have revolutionized therapy for patients with chronic myelocytic leukemia (CML), especially therapy in younger patients in the past decades. These include allogeneic hematopoietic stem cell transplantation (usually restricted to patients up to 65 years of age) and interferon (INF) therapy (which is also better tolerated in younger than in older patients). More recent studies have shown that imatinib, a tyrosine kinase inhibitor (TKI) that specifically inhibits BCR-ABL activity, is highly effective in chronic phase CML and has activity, though less reliably, in blast crisis.[1-4] In the United States, imatinib was approved for use in 2001,[1] after several years of extensive use in experimental and compassionate use protocols. Published estimates of long-term survival of patients with CML from population-based cancer registries reflect prognosis of patients diagnosed up to the early 1990s,[5] and thus do not capture the potential impact of recent advances in therapy. We aimed to disclose recent trends in and up-to-date estimates of long-term survival of CML patients by techniques of period survival analysis.[6,7] Due to the differential application of novel therapies according to age, we were specifically interested in age specific trends of prognosis.

Design and Methods

All data presented in this paper are derived from the 1973-2004 limited-use database of the Surveillance, Epidemiology,

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and End Results (SEER) Program of the United States National Cancer Institute issued in April 2006.[8] Data included in the 1973-2004 SEER database are from population based cancer registries in Connecticut, New Mexico, Utah, Iowa, Hawaii, Atlanta, Detroit, Seattle-Puget Sound and San Francisco-Oakland which together cover a population of about 30 million people. Geographical areas were selected for inclusion in the SEER Program according to their ability to operate and maintain a high-quality population-based cancer reporting system and for their epidemiologically significant population subgroups. The SEER population is comparable to the general United States population with regard to measures of poverty and education, though it tends to be more urban and has a higher proportion of foreign-born subjects than the latter.

For this analysis, all 8,475 patients aged 15 years or older with a first diagnosis of CML (and no previous cancer diagnosis) between 1980 and 2004 were selected. These patients had been followed for vital status by the SEER program (through linkage with the National Death Index data from the National Center for Health Statistics) until the end of 2004. After exclusion of 21 patients (0.25%) who were reported by autopsy only and 125 patients (1.47%) who were reported by death certificate only, there remained 8,329 patients (98.28%) for the survival analysis.

Five- and 10-year survival was calculated for the calendar periods 1990-1992, 1993-1995, 1996-1998, 1999-2001 and 2002-2004 using the period analysis methodology.[6] Furthermore, we tested for statistical significance of trends in 5- and 10-year survival between 1990-1992 and 2002-2004 by a recently described modeling approach.[7] All analyses were carried out separately for the following 5 major age groups: 15-44, 45-54, 55-64, 65-74, and 75+, which are commonly used for presentation of age specific survival and for calculation of age adjusted survival in international comparative cancer survival studies.

With period analysis, first proposed by Brenner and Gefeller in 1996,[9] only survival experience during the period of interest is included in the analysis. This is achieved by left truncation of observations at the beginning of the period in addition to right censoring at its end. The type of period analysis applied in this study is graphically illustrated in Figure 1. For example, a period estimate of 10-year survival for the 2002-2004 period is obtained by combining survival in the 1st year following diagnosis derived from patients diagnosed in 2001-2004, conditional survival in the 2nd year following diagnosis derived from patients diagnosed in 2000-2003, and so on, until conditional survival in the 10th year following diagnosis, which is obtained from patients diagnosed in 1992-1995. Period estimates of survival for the other periods are calculated analogously. It has been shown by extensive empirical evaluation that period analysis provides more up-to-date long-term survival estimates than traditional *cohort-based* survival analysis, and quite closely predicts long-term survival expectations of cancer patients diagnosed within the period of interest.[10-13] Furthermore, it has been shown that trends in 5- and 10-year survival are disclosed almost five and ten years earlier respectively than by traditional cohort survival analysis.[14] Meanwhile, the method has become an established tool for up-to-date cancer survival analysis in international collaborative studies, such as the EUROCARE study.[15,16]

According to standard practice in population-based cancer survival analysis, relative rather than absolute survival was calculated. Relative survival reflects survival of cancer patients compared to survival of the general population. It is calculated as the ratio of absolute

Years of diagnosis	Years of follow-up														
	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
1980	10														
1981	9-10	10													
1982	8-9	9-10	10												
1983	7-8	8-9	9-10	10											
1984	6-7	7-8	8-9	9-10	10										
1985	5-6	6-7	7-8	8-9	9-10	10									
1986	4-5	5-6	6-7	7-8	8-9	9-10	10								
1987	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10							
1988	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10						
1989	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10					
1990	1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10				
1991		1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10			
1992			1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10		
1993				1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10	
1994					1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10
1995						1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10
1996							1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9
1997								1	1-2	2-3	3-4	4-5	5-6	6-7	7-8
1998									1	1-2	2-3	3-4	4-5	5-6	6-7
1999										1	1-2	2-3	3-4	4-5	5-6
2000											1	1-2	2-3	3-4	4-5
2001												1	1-2	2-3	3-4
2002													1	1-2	2-3
2003														1	1-2
2004															1

Figure 1. Years of diagnosis and years of follow-up included in derivation of 10-year relative survival estimates for calendar periods 1990-1992, 1993-1995, 1996-1998, 1999-2001, and 2002-2004. The numbers within the cells indicate the years following diagnosis.

survival of cancer patients divided by the expected survival of a group of persons of the corresponding sex, age and race in the general population.[17,18] Estimates of expected survival were derived according to the so-called Ederer II method[19] using US sex, age and race specific life tables.[20]

All analyses were performed with the SAS software package using adapted versions of previously described macros for period analysis.[6,7]

Results

Numbers of cases by age group and calendar period are shown in Table 1. Overall numbers as well as age distribution were quite stable over time. The smallest and the largest group were patients aged 45-54 and 75+ (12.8% and 31.7% of all patients respectively). The latter group further increased in the two most recent periods. The number of patients exceeded 100 for each combination of age group and calendar period.

For all age groups combined, 5-year relative survival increased from 27.1% in 1990-1992 to 48.7% in 2002-2004, an increase of 21.6 percentage points (p-value for trend <0.0001, Table 2). Even stronger increases of 40.3, 32.7 and 31.2 percentage points were seen in the age groups 15-44, 45-54, and 55-64 respectively (p<0.0001 in each age group). Although survival estimates also increased in the older age groups, the increase was much less pronounced and did not reach statistical significance. In this way the age gradient in 5-year relative survival, already visible in 1990-1992, strongly increased over time. In 2002-2004, 5-year relative survival ranged from about 79.8% in the age group 15-44 to 19.7% in the age group 75+.

Table 1. Numbers of patients with chronic myelocytic leukemia by age group and calendar period.

	Calendar period					
Age	*1990-92*	*1993-95*	*1996-98*	*1999-01*	*2002-04*	*Total*
All	1,030	1,118	1,049	1,108	1,003	5,308
15-44	216	241	214	232	198	1,101
45-54	113	147	126	169	124	679
55-64	148	153	147	151	131	730
65-74	228	252	237	210	186	1,113
75+	325	325	325	346	364	1,685

Table 2. Estimates of 5- and 10-year relative survival (PE: point estimate, SE: standard error) of patients with chronic myelocytic leukemia by age groups and calendar period.

		Calendar period					
		1990-1992		*2002-2004*			
	Age	*PE*	*SE*	*PE*	*SE*	*Increase*[1]	*p-value*[2]
5-year relative survival	all	27.1	1.6	48.7	1.8	21.6	<0.0001
	15-44	39.5	3.5	79.8	3.0	40.3	<0.0001
	45-54	36.2	4.9	68.9	4.2	32.7	<0.0001
	55-64	28.8	3.9	60.0	4.7	31.2	<0.0001
	65-74	23.8	3.3	36.8	4.1	13.0	0.08
	75+	14.4	2.7	19.7	3.0	5.3	0.68
10-year relative survival	all	9.5	1.2	34.1	1.9	24.6	<0.0001
	15-44	16.1	2.8	72.4	3.5	56.3	<0.0001
	45-54	11.7	3.5	54.0	5.2	42.3	<0.0001
	55-64	7.9	2.2	33.5	5.1	25.6	<0.0001
	65-74	11.4	3.3	17.0	3.6	5.6	0.10
	75+	2.1	1.5	5.5	2.5	3.4	0.97

[1]increase from 1990-1992 to 2002-2004 in percent units; [2]p-value for trend from 1990-1992 to 2002-2004.

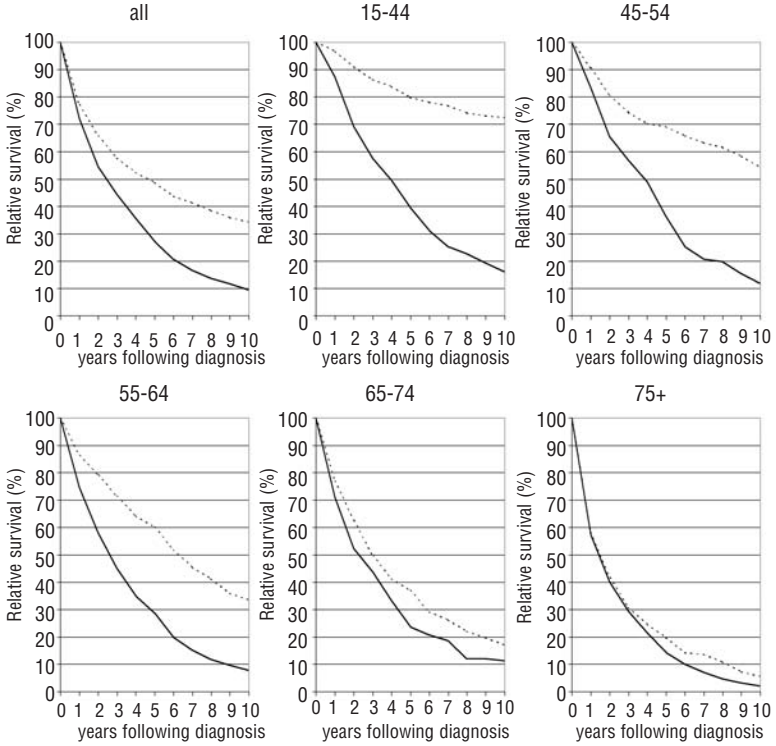

Figure 2. Ten-year relative survival curves of patients with chronic myelocytic leukemia by major age groups. Period estimates for 1990-1992 (solid curves) and 2002-2004 (dashed curves).

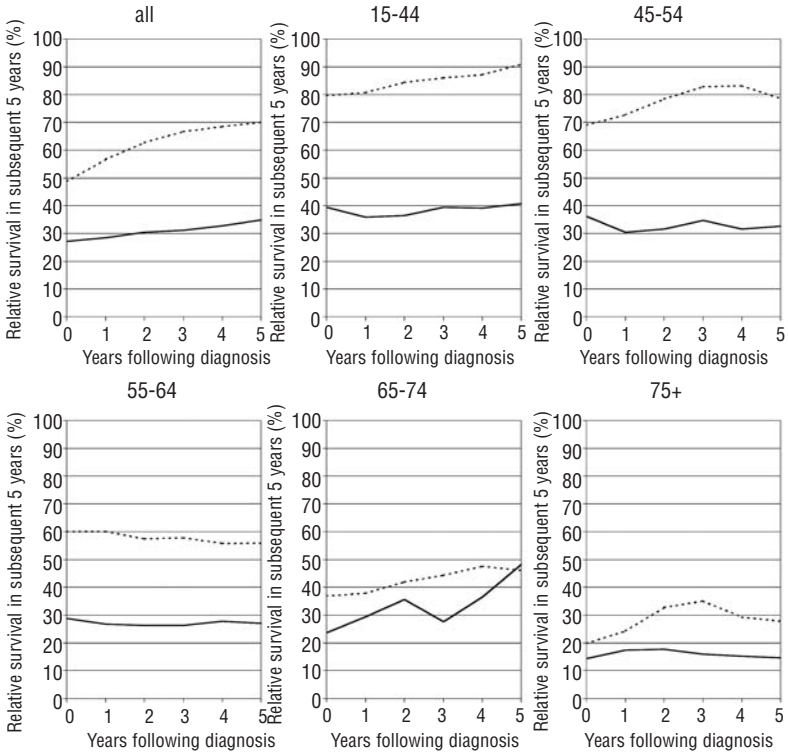

Figure 3. Conditional relative survival in subsequent five years of patients with chronic myeloid leukemia, all ages and age group 15-44, according to year following diagnosis. Period estimates for 1990-1992 (solid lines) and 2002-2004 (dashed lines).

For the two youngest age groups, the increase in 10-year relative survival from 1990-1992 to 2002-2004 was even more pronounced (+56.3 and +42.3 percent units respectively; $p<0.0001$ in both cases). Whereas only one out of 6 patients diagnosed with CML between 15 and 44 years of age was expected to survive the disease for ten years or more in 1990-1992, this proportion increased to almost 3 out of 4 in 2002-2004. A very strong, statistically significant improvement in 10-year relative survival was also seen in the age group 55-64. Nevertheless, 2 out of 3 patients were still expected to die from the disease within ten years in 2002-2004 in this age group. For age groups 65-74 and 75+, the improvement was again very modest and not statistically significant, and only one out of 20 patients with CML was expected to survive the disease for ten years or more in the oldest age group even in 2002-2004. The large differences between 5- and 10-year relative survival indicate that, in contrast to many other malignancies, a large proportion of patients with CML still die of the disease more than five years after diagnosis. This pattern particularly applies to older patients. A more comprehensive picture of the shape of the survival curves within ten years after diagnosis by age groups is shown in Figure 2. The relative survival curve does not flatten within ten years following diagnosis (as one would expect in case of cure of all surviving patients) in either age group, either in 1990-1992, or in 2002-2004. Nevertheless, improvement in survival is seen at all time points after diagnosis. This is even more evident from Figure 3, where relative survival in the subsequent five years is shown for patients who have already survived up to five years after diagnosis. For all age groups combined, relative survival in the subsequent five years was around 30% at diagnosis in 1990-1992 and hardly increased over time among patients who survived the first years after diagnosis. In 2002-2004, the initial five year relative survival of almost 50% increased to about 70% relative survival between five and ten years after

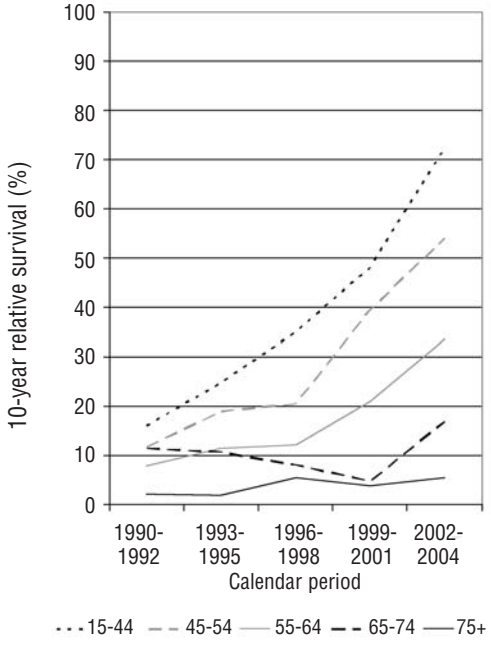

Figure 4. Period estimates of 10-year relative survival of patients with CML by major age groups in defined calendar periods from 1990-1992 to 2002-2004.

diagnosis among those patients who had survived the first five years. In age groups 15-44 and 45-54, about 90% and 80% respectively of patients surviving the first 5 years could expect to survive another five years (compared to about 40% and 30% respectively in 1990-1992). Although further survival expectations of 5-year survivors seem to have increased even in age group 75+, this pattern needs to be interpreted with caution because of the relatively high statistical uncertainty of the estimates resulting from the small numbers of 5-year survivors in this age group.

To address the question of when the strongest increase in survival was achieved for the various age groups, 10-year relative survival is shown for each of the five calendar periods under investigation in Figure 4. In age group 15-44, a strong, steady improvement was seen from calendar period to calendar period. In age groups 45-54 and 55-64, there was modest improvement between 1990-1992 and 1996-1998, followed by rapid and strong improvement in more recent years. In age group 65-74, no improvement at all was seen up to 1999-2001, but 10-year survival was strongly rising in the most recent period. In the oldest age group, 10-year relative survival remained at low levels around 5% or lower throughout the period of investigation.

Discussion

This first application of period analysis to age specific long-term survival of patients with CML discloses a dramatic improvement at an unprecedented rate for younger patients diagnosed with CML in the United States between 1990-1992 and 2002-2004. Whereas only one out of 4 CML patients was expected to be still alive five years after diagnosis in the early 1990s, this applied to one out of 2 patients in 2002-2004. Starting in the early 1990s, the improvement was most pronounced in age group 15-44, but a very strong improvement was also seen from the late 1990s onwards in age groups 45-54 and 55-64. While there is an indication that this improvement may have started to encompass age group 65-74 in the early years of the 21st century, long-term prognosis remained poor and essentially unchanged among the oldest patients.

Treatment for CML has changed significantly over the past two decades, and survival improvements seen in our analysis most likely reflect advances in treatment, including allogeneic hematopoietic stem cell transplantation and interferon (INF) therapy,[21] and, more recently, also imatinib therapy.[1]

The remarkable improvement in survival seen in younger patients does not appear to extend to older patients, particularly those over 75 years of age. Patients over 65 made up the majority (55%) of patients with CML in the years 2002-2004 and, therefore, improvements must be made in this age group in order to improve the overall outlook for patients with CML.

There are several potential overlapping reasons for the lack of improvement in survival in the oldest population of CML patients. Older patients do not qualify for allografting and do not tolerate IFN well. Furthermore, the disease may itself be different in older patients, i.e. it may be more aggressive or less responsive to therapy. In fact, age is the major prognosticator of the two most commonly used prognostic scores for CML.[22,23]

In the interpretation of our results, a number of limitations require careful consideration. Because the SEER data base does not contain information on drug treatment and SCT, the role of these factors could not be assessed directly. Although our period analysis provides more up-to-date long-term survival estimates than conventional cohort analyses, even the period estimates may still be somewhat too pessimistic as they still partly reflect the survival experience of patients first diagnosed and treated in earlier years. Therefore, long-term survival expectations of patients diagnosed in 2002-2004 may even be somewhat higher.

To summarize, the outlook for patients with CML improved dramatically between the years 1990 and 2004. This improvement is especially notable in the younger patient populations, but there is reason to expect that improvement in survival will extend to older populations as further experience in the use of TKIs for CML is accumulated[24,25] and studies delineate the safest and most effective ways to use them in older patients. Relative survival for younger patients with CML who have survived for five years is greater than 90%, suggesting that late progression is becoming a rarer event in CML and that the course of the disease may be significantly delayed.

Authorship and Disclosures

HB designed and carried out the analysis and drafted the paper; AG and DP critically reviewed and contributed to finalizing the paper. The authors reported no potential conflicts of interest.

References

1. Cohen MH, Williams G, Johnson JR, Duan J, Gobburu J, Rahmann A, et al. Approval summary for imatinib mesylate capsules in the treatment of chronic myelogenous leukemia. Clin Cancer Res 2002;8:935-42.
2. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Eng J Med 2001;344:1031-7.
3. Kantarjian H, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med 2002; 346: 645-52.
4. Hehlmann R, Hochhaus A, Baccarani M on behalf of the European LeukemiaNet. Chronic myeloid leukemia. Lancet 2007;370:342-50
5. Xie Y, Davies SM, Xiang Y, Robison LL, Ross JA. Trends in leukemia incidence and survival in the United States (1973-1998). Cancer 2003; 97: 2229-35.
6. Brenner H, Gefeller O, Hakulinen T. Period analysis for 'up-to-date' cancer survival data: theory, empirical evaluation, computational realisation and applications. Eur J Cancer 2004; 40:326-35.
7. Brenner H, Hakulinen T. Up-to-date and precise estimates of cancer

patient survival: model-based period analysis. Am J Epidemiol 2006; 164: 689-96.
8. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Limited-Use Data (1973-2004), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2007, based on the November 2006 submission.
9. Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. Cancer 1996; 78: 2004-10.
10. Brenner H, Soderman B, Hakulinen T. Use of period analysis for providing more up-to-date estimates of long-term survival rates: empirical evaluation among 370,000 cancer patients in Finland. Int J Epidemiol 2002;31:456-62.
11. Brenner H, Hakulinen T. Up-to-date long-term survival curves of patients with cancer by period analysis. J Clin Oncol 2002;20:826-32.
12. Talbäck M, Stenbeck M, Rosen M. Up-to-date long-term survival of cancer patients: an evaluation of period analysis on Swedish Cancer Registry data. Eur J Cancer 2004;40: 1361-72.
13. Ellison LF. An empirical evaluation of period survival analysis using data from the Canadian Cancer Registry. Ann Epidemiol 2006;16: 191-6.
14. Brenner H, Hakulinen T. Advanced detection of time trends in long term cancer patient survival: experience from 50 years of cancer registration in Finland. Am J Epidemiol 2002; 156:566-77.
15. Verdecchia A, Francisci S, Brenner H, Gatta G, Micheli A, Mangone L, et al. Recent cancer survival in Europe: a period analysis 2000-2002 of the EUROCARE 4 data. Lancet Oncology 2007;8:784-96.
16. Engholm G, Kejs AM, Brewster DH, Gaard M, Holmberg L, Hartley R, et al. Colorectal cancer survival in the Nordic countries and the United Kingdom: excess mortality risk analysis of 5 year relative period survival in the period 1999 to 2000. Int J Cancer 2007;121:1115-22.
17. Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. Natl Cancer Inst Monogr 1961;6:101-21.
18. Henson DE, Ries LA. The relative survival rate. Cancer 1995;76:1687-8.
19. Ederer F, Heise H. Instructions to IBM 650 programmers in processing survival computations. Methodological note No. 10. Bethesda, MD. National Cancer Institute; 1959.
20. Arias E. United States life tables, 2000. Natl Vit Stat Rep 2002;51:1-39.
21. Hehlmann R, Berger U, Pfirrmann M, Heimpel H, Hochhaus A, Hasford J, et al. Drug treatment is superior to allografting as first-line therapy in chronic myeloid leukemia. Blood 2007;109:4686-92.
22. Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-99.
23. Hasford J, Pfirrmann M, Hehlmann R, Allan NC, Baccarani M, Kluin-Nelemans JC, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon α. J Natl Cancer Inst 1998;90:850-8.
24. Rosti G, Iacobucci I, Bassi S, Castagnetti F, Amabile M, Cilloni D, et al. Impact of age on the outcome of patients with chronic myeloid leukemia in late chronic phase: results of a phase II study of the GIMEMA CML Working Party. Haematologica 2007;92:101-5.
25. Cortes J, Talpaz M, O'Brien S, Giles F, Beth Rios M, Shan J, et al. Effects of age on prognosis with imatinib mesylate therapy for patients with Philadelphia chromosome-positive chronic myelogenous leukemia. Cancer 2003;98:1105-13.