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Letter to Blood

TO THE EDITOR:

Trends in survival of young adult patients with acute lymphoblastic leukemia in Sweden and the United States

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The survival of children with acute lymphoblastic leukemia (ALL) has improved since the 1970s because of continuous fine-tuning of treatment protocols based on a series of randomized clinical trials.[1,2] Alas, despite more precise risk stratification and widespread implementation of aggressive treatment protocols, results in adults have not been as promising.[3] For example, the 5-year relative survival of adult ALL patients diagnosed from 2002 to 2006 in Germany and the United States of America was 43.4% and 35.5%, respectively.[4] Although survival was better in patients aged 15 and 24 years, with 5-year relative survival of 59.2% (Germany) and 54.9% (United States), the lack of curative treatment of many adult patients is disconcerting. Poorer outcomes for adolescent and young adult patients have been attributed to lower rates of enrollment in clinical trials, although there is recent evidence of improved enrollment rates for these patients.[5] There is an ongoing shift in the treatment of younger adult ALL patients in high-resource countries with increasing use of pediatric or pediatric-inspired protocols (in Sweden's Nordic Society for Pediatric Hematology and Oncology Protocol for Childhood Acute Lymphoblastic Leukemia Intermittent Versus Continuous PEG Asparaginase [NOPHO ALL2008] protocol) up to age 45, as well as the introduction of imatinib and later-generation tyrosine kinase inhibitors for patients with Philadelphia-positive or Philadelphia-like ALL.[6,7]

We read with great interest the Cancer and Leukemia Group B 10403 study recently reported in this journal.[8] The authors stated that the "use of a pediatric regimen for young adults with ALL up to age 40 years was feasible and effective, resulting in improved survival rates compared to historical controls." Their results motivated us to compare, in a population-based setting, temporal trends in relative survival of ALL patients in Sweden and the United States Surveillance, Epidemiology and End Results (SEER) database, with emphasis on younger adults.

We identified all patients diagnosed with ALL between 1 January 1980 and 31 December 2015 in the Swedish Cancer Register (Table 1), which is maintained by the National Board of Health and Welfare and was founded in 1958 and covers all of Sweden.[9,10] All physicians and pathologists/cytologists are obliged by law to report each occurrence of cancer to the registry. Patients were followed from the date of diagnosis until death, emigration, or end of follow-up (31 December 2017), whichever occurred first. The choice to include patients from 1980 was because coding practices have been consistent since 1980.

Using a case-listing session in the SEER*Stat software,[11] we identified all patients diagnosed with ALL between 1973 and 2015 based on the SEER 9 database of the Surveillance, Epidemiology, and End Results (SEER) Program of the United States National Cancer Institute.[12] Patients were followed to the end of 2015. The SEER 9 database covered 9.4% of the US population in 2010[13] and is based on geographical areas selected for their ability to operate and maintain high-quality population-based cancer-reporting systems and for their epidemiologically significant population subgroups. The SEER population is similar to that of the general US population in terms of racial and ethnic makeup, although it may be more affluent than average[14] and deliberately oversamples some racial and ethnic minorities including Hispanics, Asians, and Pacific Islanders.[13]

Relative survival ratios (RSRs) were estimated as measures of net survival.[15,16] An important advantage of the relative survival framework is that it provides a measure of excess mortality associated with a diagnosis of cancer without relying on classification of cause of death. We estimated relative survival using flexible parametric relative survival models.[17] For the main analysis, we predicted temporal trends in 1- and 5-year relative survival for patients in age groups 18 to 29, 30 to 44, 45 to 64, and 65 to 84 years. This model was restricted to the first 6 years of follow-up and to patients aged 45 years and older at diagnosis. We restricted follow-up to 6 years, rather than 5, to improve the stability of 5-year survival estimates. Time since diagnosis and year of diagnosis were modeled using natural splines with 6 and 2 degrees of freedom, respectively. The model included an interaction between age and year. All main effects and the interaction were time-dependent (effectively relaxing assumptions of nonproportional excess hazards). Results are presented for both sexes combined, because sex-specific analyses showed similar results. Analyses were performed using Stata release 15.1 (College Station, TX: StataCorp LLC).

There was a male dominance in both the Swedish (56%) and US cohorts (58%; Table 1). Patients diagnosed in the 65 to 84 year age group constituted 32% in Sweden and 25% in the United States, leading to a slightly higher median age at

Table 1. Characteristics of patients diagnosed with ALL in the United States (SEER) and Sweden

	1980-1986		1987-1991		1992-1996		1997-2001		2002-2015		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Sweden												
Male	150	56	126	62	113	55	121	54	371	56	881	56
Female	120	44	76	38	92	45	105	46	288	44	681	44
Total	270	100	202	100	205	100	226	100	659	100	1562	100
Age, y												
18-29	57	21	35	17	41	20	43	19	129	20	305	20
30-44	51	19	42	21	34	17	44	19	146	22	317	20
45-64	69	26	53	26	64	31	71	31	181	27	438	28
65-84	93	34	72	36	66	32	68	30	203	31	502	32
Total	270	100	202	100	205	100	226	100	659	100	1562	100
Median age, y	56		54		53		53		52		53	
Allogeneic stem cell transplantations, no.												
Ages 18-45, y	14		20		32		56		182		304	
Ages 46+, y	0		1		6		21		89		117	
United States (SEER-9)												
Male	425	62	396	61	383	59	394	58	1381	56	2979	58
Female	266	38	248	39	268	41	285	42	1078	44	2145	42
Total	691	100	644	100	651	100	679	100	2459	100	5124	100
Age group, y												
18-29	207	30	137	21	161	25	156	23	525	21	1186	23
30-44	138	20	144	22	150	23	149	22	499	20	1080	21
45-64	168	24	173	27	160	25	216	32	862	35	1579	31
65-84	178	26	190	30	180	28	158	23	573	23	1279	25
Total	691	100	644	100	651	100	679	100	2459	100	5124	100
Median age, y	45		50		46		48		50		49	
Race												
White	599	87	555	86	549	84	557	82	1911	78	4171	81
Black	43	6	40	6	47	7	44	6	218	9	392	8
Other	47	7	49	8	54	8	75	11	314	13	539	11
Unknown	2	0	0	0	1	0	3	0	16	1	22	0
Total	691	100	644	100	651	100	679	100	2459	100	5124	100

diagnosis in Sweden (Table 1). The number of allogeneic transplants increased 2.3 times in younger (18-45 years) and 3.1 times in older (46+ years) Swedish patients between the last 2 calendar periods. Starting in the mid-1990s, there was a gradual increase in 5-year RS of patients aged 30-44 years in both cohorts; 5-year RSRs were predicted to be 0.67 (95% Confidence Interval [CI], 0.54-0.77; Sweden) and 0.60 (95% CI, 0.51-0.68; SEER) in patients diagnosed in 2015 (Figure 1). The corresponding 5-year RSRs in patients diagnosed in 1990 were 0.26 (95% CI, 0.20-0.33) and 0.25 (95% CI, 0.21-0.28). The steepest increase in relative survival was observed in Swedish patients diagnosed between 2005 and 2015. In 18- to 29-year-old patients, the improvement in 5-year relative survival (RS) started 5 to 10 years earlier and increased faster in Swedish patients, with 5-year RSRs predicted to be 0.71 (95% confidence interval, 0.56-0.81; Sweden) and 0.62 (95% confidence interval, 0.53-0.70; SEER) in patients diagnosed in 2015, respectively. A similar but not so clear pattern observed regarding 1-year RS for both age groups (supplemental Material, available on the *Blood* Web site). Smaller improvements in RS were observed in age groups 45 to 64 and 65 to 84 years diagnosed in the most recent decade.

We believe these improvements in survival confirm, importantly, also in a population-based setting, that pediatric-inspired regimens used in young adult ALL patients improve survival.[6,18,19] Stock et al[8] compared outcomes in patients treated between 2007 and 2012 with historical controls without adjusting for improvements observed over time in the general population. In this analysis, we chose to use RS on population-based cohorts to minimize the effect such biases. The superior cure rate for children has been suggested to be related to differences in disease biology and chemosensitivity as well as better treatment tolerance, physician compliance, and patient adherence in the pediatric patient population.[6] In the Nordic countries, NOPHO ALL2008 was introduced for patients aged 1 to 45 years with Philadelphia chromosome negative B-cell precursor or T-lineage ALL.[7] The main difference between previous protocols for adults and this pediatric protocol includes extensive use in all risk groups of asparaginase and high-dose methotrexate with coadministration of mercaptopurine. These and RS modifications have clearly

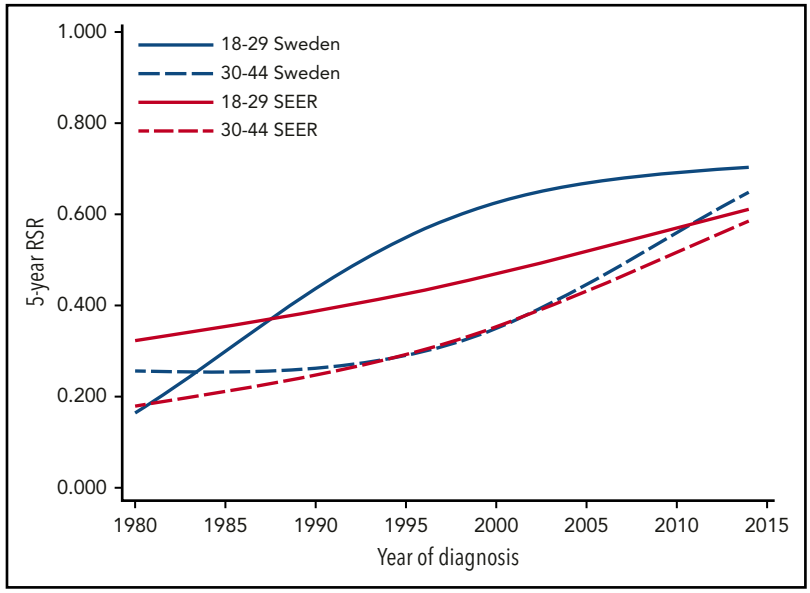

Figure 1. Trends in 5-year relative survival for ALL patients diagnosed in the United States (SEER) and Sweden.

contributed to the improved survival observed in the young adult Swedish patients. The next generation of pediatric ALL treatment protocols should be followed closely by physicians also taking care of young adult patients.[20]

Authorship

Contribution: M.B., G.E., and P.W.D. designed the study; P.W.D. gathered the data; P.W.D. and G.E. performed the statistical analyses; all authors analyzed and interpreted the data; M.B. and P.W.D. wrote the first draft; and all authors approved the final manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Footnotes

Technical details of the analyses and code for reproducing the analysis can be found at http://pauldickman.com/all/.

The online version of this article contains a data supplement.

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DOI 10.1182/blood.2019001168