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ORIGINAL REPORT

Improved Survival for Children and Adolescents With Acute Lymphoblastic Leukemia Between 1990 and 2005: A Report From the Children's Oncology Group

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ABSTRACT

Purpose
To examine population-based improvements in survival and the impact of clinical covariates on outcome among children and adolescents with acute lymphoblastic leukemia (ALL) enrolled onto Children's Oncology Group (COG) clinical trials between 1990 and 2005.

Patients and Methods
In total, 21,626 persons age 0 to 22 years were enrolled onto COG ALL clinical trials from 1990 to 2005, representing 55.8% of ALL cases estimated to occur among US persons younger than age 20 years during this period. This period was divided into three eras (1990-1994, 1995-1999, and 2000-2005) that included similar patient numbers to examine changes in 5- and 10-year survival over time and the relationship of those changes in survival to clinical covariates, with additional analyses of cause of death.

Results
Five-year survival rates increased from 83.7% in 1990-1994 to 90.4% in 2000-2005 ($P < .001$). Survival improved significantly in all subgroups (except for infants age ≤ 1 year), including males and females; those age 1 to 9 years, 10+ years, or 15+ years; in whites, blacks, and other races; in Hispanics, non-Hispanics, and patients of unknown ethnicity; in those with B-cell or T-cell immunophenotype; and in those with National Cancer Institute (NCI) standard- or high-risk clinical features. Survival rates for infants changed little, but death following relapse/disease progression decreased and death related to toxicity increased.

Conclusion
This study documents ongoing survival improvements for children and adolescents with ALL. Thirty-six percent of deaths occurred among children with NCI standard-risk features emphasizing that efforts to further improve survival must be directed at both high-risk subsets and at those children predicted to have an excellent chance for cure.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy, comprising 25% of cancers occurring before age 15 years and 19% among those younger than age 20 years.[1] The 5-year survival rate increased from less than 10% in the 1960s to 77% in 1985 to 1994.[1] Survival rate has continued to increase over the past 10 to 15 years.[2-11] The National Cancer Institute (NCI) SEER Program reported that 5-year survival for US patients younger than age 15 years with ALL increased from 80.2% to 87.5% between 1990-1994 and 2000-2004.[12] Five-year survival rates for adolescents age 15 to 19 years increased from 41.0% in 1980-1984 to 61.1% in 2000-2004.[13]

The Children's Oncology Group (COG) includes more than 200 member institutions in the United States, Canada, Australia, and New Zealand. Unlike the SEER system, which tracks outcome in five representative states and four metropolitan areas that include approximately 10% of the US population, COG data include patients from all areas of the United States and Canada and provide an opportunity to assess outcome for children with ALL throughout these countries and to examine the prognostic impact of covariates not included in registry data. We report changes in survival among children enrolled onto COG ALL clinical trials between 1990 and 2005 and the extent to which different clinical and biologically defined patient subgroups benefited from treatment improvements.

PATIENTS AND METHODS

Patients

In all, 21,626 eligible children and adolescents younger than age 22 years enrolled onto one of 36 COG ALL clinical trials (Appendix Table A1, online only) between January 1, 1990, and December 31, 2005. Patients were treated on clinical trials that tested treatment intensifications and the need for cranial irradiation, and they used clinical and biologic prognostic variables, including genetic subtype and early treatment response, to risk stratify patients and assign therapies of varying intensity.[18] We divided this period into three eras that included similar numbers of patients: 1990-1994 (7,304 patients; median follow-up, 9.13 years), 1995-1999 (7,169 patients; median follow-up, 8.02 years), and 2000-2005 (7,153 patients; median follow-up, 5.35 years). Most patients (92.2%) were treated in the United States, with 5.8% in Canada, and 2% elsewhere. Patients and/or a parent/guardian provided informed consent for clinical trial participation; trials were approved by institutional review boards at COG centers. We analyzed outcome on the basis of clinical features, including age and WBC count at diagnosis, sex, immunophenotype, race, and ethnicity as reported by the patient or parent.

Statistical Analyses

Overall survival estimates were obtained by using the Kaplan-Meier method,[19] with SEs calculated by using the method of Peto and Peto.[20] Survival time was calculated as the time from study entry to death or date of last contact. Comparisons of survival curves were performed by using the log-rank test.[21] Survival curves were truncated at year 15. The cumulative incidence of death due to various causes was determined after adjusting for competing risks.[22] Multivariate Cox regression analysis was used to identify prognostic factors affecting overall survival. Survival tree regression was used in both infant and non–infant subsets to identify prognostic factors and explore their association with overall survival.[23,24] Data were frozen in September 2009.

Incidence rates for ALL were determined by using published SEER data with additional information on rates obtained directly from the National Institutes of Health and Information Management Services. Total numbers of ALL cases expected to occur in the United States during specific time periods was determined by applying these incidence rates to population statistics derived from US census data.

RESULTS

Overall 5- and 10-year survival rates increased significantly over time (Fig 1; $P < .001$). Five-year survival increased from 83.7% (SE, 0.4%) in 1990-1994 to 87.7% (SE, 0.4%) in 1995-1999 and to 90.4% (SE, 0.5%) in 2000-2005 (Table 1). Similar increases were seen in 10-year survival between 1990-1994 (80.1%; SE, 0.8%) and 1995-1999 (83.9%; SE, 1.3%; $P < .001$). For the eras from 1990 to 1999, approximately 84% of deaths occurred within 5 years of diagnosis and only 1% occurred more than 10 years following diagnosis (Appendix Tables A2 to A6, online only). Because of these factors and the more limited follow-up for the 2000-2005 era, subsequent analyses focused on 5-year survival.

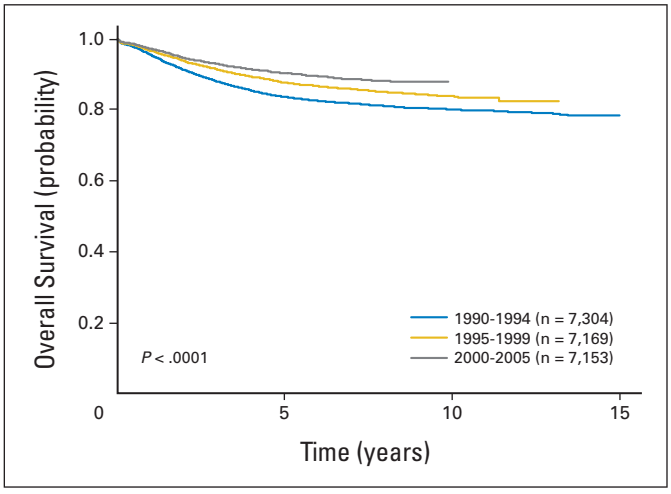

Fig 1. Overall survival probability by treatment era for patients enrolled onto Children's Oncology Group trials in 1990-1994, 1995-1999, and 2000-2005.

Survival improved significantly in all subgroups examined except for infants ≤ 1 year old (Table 1 and Appendix Figs A1 to A6, online only): ages 1 to 9 years, 10+ years, and 15+ years; males and females; self-reported whites, blacks, and other races; self-reported Hispanics, non-Hispanics, and persons of unknown ethnicity; those with B-cell and T-cell ALL; and those with standard-risk (age 1 to 9.99 years; initial WBC $< 50{,}000/\mu L$) or high-risk (age ≥ 10 years and/or initial WBC $\geq 50{,}000/\mu L$) features by using NCI/Rome[25] criteria. The relative reductions in 5-year risk of death between the 1990-1994 and 2000-2005 eras were similar in all non–infant subgroups examined, ranging from 30% to 50% (Table 1). Because the results for infants differed from those of older children, we also analyzed data separately for infants and non–infants (Appendix Tables A7 and A8, online only).

Deaths that occurred after induction failure or relapse were classified as leukemia related, and those that occurred without prior induction failure or relapse were deemed treatment related (Table 2 and Appendix Tables A9 and A10, online only). Among all patients, the 5-year cumulative incidence of death decreased from 16.35% in 1990-1994 to 9.6% in 2000-2005 ($P < .001$), and the 10-year cumulative incidence of death decreased from 19.86% in 1990-1994 to 16.07% in 1995-1999 ($P < .001$). This decrease was primarily due to reduction in the 5-year cumulative incidence of death following relapse/disease progression from 12.83% in 1990-1994 to 7.22% in 2000-2005 ($P < .001$), with similar reductions in 10-year rates between 1990-1994 and 1995-1999. Among infants (Appendix Table A9), the 5-year cumulative incidence of death changed little between 1990-1994 and 2000-2005 (52.1% *v* 50.3%; $P = .45$), but the causes of death changed considerably. The 5-year cumulative incidence of death following relapse/disease progression decreased from 43% in 1990-1994 to 27.2% in 2000-2005 ($P < .001$), and the cumulative incidence of treatment-related death increased from 3.9% in 1990-1994 to 13.9% in 2000-2005 ($P < .001$).

The highest relative risks of death occurred in known high-risk subgroups (Table 3). The relative risk of death was 2.3-fold (1990-1994) to 3.1-fold (2000-2005) higher for patients age 10+ years versus those age 1 to 9.99 years. The differences were even larger when those age 1 to 9.99 years were compared with infants age ≤ 1 year and adolescents age ≥ 15 years. We observed modest but statistically significant sex-based differences in survival, with males having a relative risk of death 1.2- to 1.3-fold higher than that of females. Self-described blacks had an increased relative risk of death compared with whites. Although information about ethnicity was not available for approximately 30% (6,509 of 21,626) of patients, self-described Hispanics (n = 2,589) had a higher relative risk of death than non-Hispanics. Leukemia immunophenotype was prognostic, with patients who had T-cell ALL having a higher relative risk of death than those with B-cell ALL. Patients with NCI high-risk ALL had a 2.4- to 3.6-fold higher relative risk of death than those with standard-risk

Table 1. Five-Year Overall Survival of Patient Subsets by Era

Patient Group	No.	5-Year Survival ± SE (%) 1990-1994	No. of Patients	1995-1999	No. of Patients	2000-2005	No. of Patients	% Reduction 2000-2005 *v* 1990-1994	*P**
All patients	21,626	83.7 ± 0.4	7,304	87.7 ± 0.4	7,169	90.4 ± 0.5	7,153	41	< .001
Age group, years									
< 1	461	47.9 ± 4.1	154	48.1 ± 4.3	148	53.2 ± 5.4	159	10	.4520
1-9.99	16,578	88.2 ± 0.4	5,599	91.7 ± 0.4	5,523	94.1 ± 0.4	5,456	50	< .001
≥ 10	4,587	70.8 ± 1.2	1,551	76.9 ± 1.2	1,498	81.6 ± 1.3	1,538	37	< .001
10-14.99	3,072	72.8 ± 1.4	1,094	78.9 ± 1.4	1,001	84.7 ± 1.5	977	44	< .001
≥ 15	1,515	66.1 ± 2.3	457	72.9 ± 2.2	497	75.9 ± 2.6	561	29	.0025
Sex									
Male	12,155	82.7 ± 0.6	4,117	86.3 ± 0.6	4,057	89.9 ± 0.6	3,981	42	< .001
Female	9,471	84.9 ± 0.7	3,187	89.5 ± 0.6	3,112	91.0 ± 0.7	3,172	40	< .001
Race									
White	15,759	86.3 ± 0.5	5,410	88.9 ± 0.5	4,890	91.1 ± 0.5	5,242	35	< .001
Black	1,474	75.3 ± 2.0	535	80.7 ± 1.9	472	87.8 ± 2.1	425	51	< .001
Other	4,393	77.0 ± 1.2	1,359	86.3 ± 0.9	1,807	88.1 ± 1.2	1,486	48	< .001
Ethnicity									
Hispanic	2,589	82.0 ± 1.8	547	86.2 ± 1.4	675	87.6 ± 1.2	1,367	31	.0076
Non-Hispanic	12,528	87.0 ± 0.6	3,626	88.5 ± 0.6	3,377	91.4 ± 0.5	5,525	34	< .001
Unknown	6,509	80.0 ± 0.7	3,131	87.1 ± 0.6	3,117	83.6 ± 3.0	261	18	< .001
Immunophenotype									
B cell	16,880	84.9 ± 0.5	5,068	88.3 ± 0.4	5,830	91.1 ± 0.5	5,982	41	< .001
T cell	1,831	70.7 ± 1.7	748	80.7 ± 1.7	624	81.6 ± 2.2	459	37	< .001
NCI risk group									
Standard risk	14,154	90.2 ± 0.5	4,624	92.7 ± 0.4	4,674	95.0 ± 0.4	4,856	49	< .001
High risk		73.8 + 0.9	2,680	79.8 ± 0.9	2,494	82.9 ± 1.1	2,286	32	< .001

Abbreviation: NCI, National Cancer Institute.
*The *P* values were computed by comparing the survival curves among all three eras.

ALL. However, because most patients have NCI standard-risk clinical features, a significant proportion of deaths occurred among the favorable prognosis subgroups (Table 4). Five-year survival of patients with NCI standard-risk ALL was 90% to 95% between 1990 and 2005 (Table 1 and Appendix Fig A6A), but approximately 36% of total deaths occurred among this subset.

For patients older than age 1 year, era, sex, race, immunophenotype, and NCI risk group were all significant prognostic factors in the multivariate Cox regression model (Table 5). To better understand the most important factors predicting risk of death, we performed survival tree regression modeling (Appendix Fig A7A, online only). This analysis showed that NCI risk group was the most significant overall prognostic factor. Among NCI standard-risk patients, era (2000-2005 *v* 1990-1999) was the most significant prognostic factor. For NCI high-risk patients, age (1 to 14.99 *v* ≥ 15 years) was the most prognostic factor. Among NCI high-risk patients younger than age 15 years, race was the most significant prognostic factor, with survival for black/other being inferior to that of whites. For adolescents age ≥ 15 years,

Table 2. Cumulative Incidence of Death After Relapse/Disease Progression *v* Death As a First Event in COG ALL Trials

Death As a First or Subsequent Event	Cumulative Incidence (%) 1990-1994	1995-1999	2000-2005	Overall	*P**
5-year					
Relapse/disease progression or secondary malignancies as first event	12.83	9.03	7.22	9.82	< .001
Treatment-related death prior to relapse/disease progression	2.16	1.92	1.57	1.89	.0335
Unknown or unrelated	1.37	1.36	0.81	1.19	.0013
Overall	16.35	12.31	9.60	12.90	< .001
10-year					
Relapse/disease progression or secondary malignancies as first event	15.80	12.45	—	12.98	< .001
Treatment-related death prior to relapse/disease progression	2.17	1.95	—	1.91	.3413
Unknown or unrelated	1.89	1.67	—	1.61	.7149
Overall	19.86	16.07		16.50	< .001

Abbreviations: ALL, acute lymphoblastic leukemia; COG, Children's Oncology Group.
**P* values in the 5-year category were computed by comparing the corresponding cumulative incidence curves among all three eras; *P* values in the 10-year category were for comparison between the first two eras (1990-1994 *v* 1995-1999).

Table 3. Five-Year RR of Death by Era and Characteristic

Patient Group	Era					
	1990-1994		1995-1999		2000-2005	
	RR	*P*	RR	*P*	RR	*P*
Age, years						
1-9.99	1.0		1.0		1.0	
≥ 10	2.26	< .001	2.40	< .001	3.10	< .001
≥ 15	2.61	< .001	2.65	< .001	3.97	< .001
< 1	3.65	< .001	4.92	< .001	7.81	< .001
Sex						
Female	1.0		1.0		1.0	
Male	1.17	< .001	1.34	< .001	1.16	.0213
Race*						
White	1.0		1.0		1.0	
Black	1.73	< .001	1.60	< .001	1.37	.0119
Other	1.58	< .001	1.16	.0121	1.27	.0056
Ethnicity*						
Non-Hispanic	1.0		1.0		1.0	
Hispanic or Latino	1.31	.0024	1.16	.0645	1.47	< .001
Immunophenotype						
B cell	1.0		1.0		1.0	
T cell	1.75	< .001	1.46	< .001	2.04	< .001
NCI risk group†						
Standard risk	1.0		1.0		1.0	
High risk	2.42	< .001	2.52	< .001	3.59	< .001

NOTE. *P* values compare RR of the death to the baseline value defined as RR of 1.0 for each characteristic.
Abbreviations: NCI, National Cancer Institute; RR, relative risk.
*Self-reported race or ethnicity.
†Standard, age 1-9.99 years and initial WBC < 50,000/μL; high, age ≥ 10 years and/or initial WBC ≥ 50,000/μL.

era was the most significant prognostic factor, with better survival rates in 1995-2005 compared with 1990 to 1994.

For infants, age considered as a continuous variable was the most important prognostic factor (Appendix Fig A7B). The best age cutoff among infants was 92 days, with 5-year survival rates of 57.8% and 25.6% for age ≥ 92 days and less than 92 days, respectively ($P < .001$). Among infants ≥ 92 days old, WBC was the most significant predictor of survival, with higher WBC resulting in poorer outcome.

DISCUSSION

This study, which includes the largest childhood ALL cohort ever reported, documents progressive improvements in survival for children with ALL enrolled onto COG clinical trials between 1990-1994 and 2000-2005. Five-year survival increased from 83.7% to 90.4% during this time. The improved survival was explained primarily by an approximately 44% decrease in the risk of death following relapse/disease progression. Although we examined overall and not event-free survival (EFS) and cannot comment directly on changes in the incidence of relapse, a study of almost 10,000 children treated on COG ALL trials between 1988 and 2002, including 1,961 who relapsed, showed no significant improvements in survival after relapse over time.[26] Taken together with results of COG ALL clinical trials showing significant improvements in EFS during this period, we believe that the major reason for improved survival was decreased risk of relapse.[14,15,17]

Our cohort includes 18,501 (55.8%) of 33,139 US ALL cases in persons age 0 to 14.99 years predicted to occur between 1990 and 2005. Thus, our results are representative of survival following contemporary therapy in the United States and are consistent with previous reports of outcomes for children younger than age 15 years diagnosed with cancer between 1990 and 1994 enrolled onto COG trials.[27,28] In contrast, only approximately 25% of adolescents age 15 to 19 years diagnosed with cancer were enrolled onto COG trials between 1990 and 1994.[27] Our data are similar, with 33.5% (1,392 of 4,159) of US adolescents age 15 to 19.99 years predicted to develop ALL between 1990 and 2005 enrolling onto COG trials. There are a variety of reasons that children and adolescents with ALL might not be included in COG ALL trials, including participation in trials conducted by other centers,[6,8] lack of an open study at the time of diagnosis, having the patient/parent decline participation, or failure to meet eligibility criteria. Most US children with ALL still enroll onto COG trials. In 2009, 1,951 (68%) of 2,869 US children and adolescents age 0 to 19.99 years predicted to develop ALL enrolled onto a COG trial, including 1,758 (69%) of 2,540 of those age 0 to 14.99 years and 168 (51%) of 329 of those age 15 to 19.99 years. The number of older adolescents with ALL enrolling onto COG trials has increased over time, which is an important trend, given the higher survival rates obtained with pediatric versus adult ALL trials for this age group.[29-31]

Pulte et al[12,13] reported survival for US children and adults diagnosed with ALL between 1990 and 2004 by using the SEER 9 Registries database, which includes about 30 million people. Our results show higher survival rates than the SEER-estimated 5-year survival of 87.5% from 2000-2004 for children younger than age 15 years and 61.1% for those age 15 to 19 years. We found 5-year survival rates of 91.4% for US children younger than age 15 years and 74.5% for those age 15 to 19 years in 2000-2005. It is unlikely that the slight difference in time period analyzed (SEER: 2000-2004 *v* COG: 2000-2005) accounts for these differences. There may be differences based on clinical trial enrollment because the SEER data include all patients reported to tumor registries in the specified areas, although the COG data are based on patients who met eligibility criteria and were offered and accepted clinical trial enrollment. The SEER 9 population is more urban and includes a higher percentage of foreign-born persons than the overall US population; these differences might contribute to observed differences in survival. There was a 13% absolute survival advantage for older adolescents in this COG cohort compared with the SEER estimates, consistent with the significant survival advantages for older adolescents with ALL treated on COG versus adult cooperative group trials.[29] These data emphasize that optimal treatment for an older adolescent with ALL is referral to a pediatric center and enrollment onto a pediatric cooperative group trial.

In our analyses, survival improvements occurred in every subgroup analyzed with the exception of infants age ≤ 1 year (Table 1 and Appendix Figs A1 to A6). The magnitude of the decrease in risk of death between 1990-1994 and 2000-2005 was generally similar among non–infant subgroups and ranged from approximately 30% to 50%.

There were no survival improvements for infants enrolled onto COG ALL trials between 1990 and 2005 (Appendix Fig A1A). Infants contributed disproportionately to deaths because they accounted for only 2.1% (461 of 21,626) of patients but 8.0% (231 of 2,878) of deaths ($P < .001$). During this period, the COG pursued several strategies to attempt to increase survival for infants with ALL. Chemotherapy treatment was intensified significantly in the Children's Cancer Group

Table 4. Number of Deaths by Era and Presenting Characteristics

Patient Group	Total No. of Patients	Projected No. of Deaths in 5 Years							
		1990-1994		1995-1999		2000-2005		1990-2005	
		No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
All patients	21,626	1,194	100	882	100	687	100	2,763	100
Age group, years									
≤ 1	461	80	6.7	77	8.7	74	10.8	231	8.4
1-9.99	16,578	662	55.5	461	52.0	324	46.9	1,447	52.2
≥ 10	4,587	453	37.9	346	39.2	283	41.3	1,082	39.1
10-14.99	3,072	298	24.9	211	24.0	150	21.8	659	23.8
≥ 15	1,515	155	13.0	135	15.3	135	19.7	425	15.4
Sex									
Male	12,155	714	59.8	557	63.0	402	58.6	1,673	60.5
Female	9,471	480	40.2	326	37.1	285	41.6	1,091	39.6
Race									
White	15,759	727	60.9	547	61.9	493	71.8	1,767	63.9
Black	1,474	129	10.8	101	11.4	53	7.7	283	10.2
Other	4,393	341	28.6	235	26.7	141	20.6	717	26.0
Ethnicity									
Hispanic	2,589	98	8.2	93	10.5	170	24.7	361	13.1
Non-Hispanic	12,528	470	39.4	388	43.9	473	69.0	1,331	48.2
Unknown	6,509	626	52.4	402	45.6	43	6.3	1,071	38.7
Immunophenotype									
B cell	16,895	768	64.3	684	77.5	537	78.1	1,989	72.0
T cell		1,831		121	13.7	84	12.3	424	15.3
NCI risk group									
Standard	14,002	438	36.7	323	36.6	233	34.0	994	36.0
High	7,154	677	56.7	484	54.9	366	53.3	1,527	55.3

Abbreviation: NCI, National Cancer Institute.

(CCG) 1953 and COG P9407 trials, and the use of stem-cell transplantation in first remission was explored for those with *MLL* gene rearrangements. Stem-cell transplantation was not beneficial for infants in these COG ALL trials,[16] and treatment intensification shifted the causes of death, with a significant decrease in death following relapse/disease progression but a parallel increase in death related to toxicity, with no net improvement in survival (Appendix Table A9). The Interfant99 infant ALL trial (1999-2005) obtained results similar to those of the COG trials, with 4-year EFS of only 48%.[32] Although Interfant99 showed a benefit for stem-cell transplantation among a select high-risk subgroup of infants, survival was still poor for these patients.[33] Infant ALL is a unique high-risk subset that requires new therapeutic strategies.

Table 5. Multivariate Cox Regression Analysis for Patients Older Than Age 1 Year

Variable	HR	95% CI	*P*
Sex			
Female *v* male	0.83	0.77 to 0.90	< .001
Race			
White *v* black	0.84	0.73 to 0.97	.0208
White *v* other	0.64	0.56 to 0.72	< .001
Age, years			
1-9 *v* 15+	0.53	0.46 to 0.60	< .001
10-14 *v* 15+	0.71	0.63 to 0.81	< .001
NCI risk group			
Standard *v* high	0.48	0.42 to 0.53	< .001
Immunophenotype			
B cell *v* T cell	0.76	0.68 to 0.84	< .001
Era			
1995-1999 *v* 1990-1994	0.73	0.67 to 0.80	< .001
2000-2005 *v* 1990-1995	0.56	0.50 to 0.62	< .001

Abbreviation: HR, hazard ratio; NCI, National Cancer Institute.

Survival for self-reported blacks with ALL improved significantly during the eras examined. The absolute difference in 5-year survival between blacks and whites decreased from 11.0% in 1990-1994 to 3.3% in 2000-2005. There are race-based differences in ALL biology, with blacks having a higher incidence of T-cell ALL and other high-risk features.[34] Among the COG patients, 17.7% of blacks versus 9.5% of whites had T-cell ALL ($P < .001$) and 44.5% of blacks had NCI high-risk features versus 32.9% of whites ($P < .001$). Thus, black children and adolescents with ALL are predicted to have an inferior survival compared with whites because of the different percentages of ALL subtypes in the two racial groups. However, within these ALL subtypes, although patient numbers are small, our results show decreases in the racial outcome gap between 1990-1994 and 2000-2005. The absolute difference in 5-year survival for blacks versus whites with T-cell ALL decreased from 5.0% in 1990-1994 (94 blacks) to 0.02% in 2000-2005 (57 blacks). Similarly, for children with NCI high-risk B-cell ALL, the gap decreased from 11.1% in 1990-1994 (129 blacks) to 6.6% in 2000-2005 (53 blacks).

Self-described ethnicity is another important risk factor in childhood ALL. Hispanics have inferior outcomes to non-Hispanics.[35] Our

study confirms this observation, with some differences in the magnitude of differences in the three eras (Tables 1 and 3). Importantly, there was much greater capture of information regarding self-described ethnicity in 2000-2005, with only 3.6% (261 of 7,153) of unknown ethnic group compared with 43.2% (6,284 of 14,473) in 1990-1999. We observed a 1.5-fold higher risk of death for Hispanics versus non-Hispanics in 2000-2005. A variety of reasons might account for the inferior outcome of Hispanics. For example, recent investigations have shown a much higher incidence of certain high-risk leukemia cell genomic alterations in Hispanics enrolled onto COG ALL trials.[36]

Simple demographic and clinical prognostic factors can identify patient subsets with significantly increased risk of death: infants, adolescents age ≥ 10 or ≥ 15 years, T-cell ALL, and NCI high-risk ALL. The relative risks of death for these subsets ranged from about two- to eight-fold higher than for lower-risk subsets (Table 3). However, 36% of total deaths occurred among patients with NCI standard-risk ALL. Thus, efforts to decrease ALL deaths must focus both on high-risk patient subsets and on the large subset of patients with favorable clinical characteristics. Detailed biologic characterization of lymphoblasts and host germline variability and sophisticated measurements of early treatment response can improve identification of ultra-low-risk patient subsets and identify patients at high risk of treatment failure.[18,36-47]

We analyzed whether death occurred as a first event or after relapse/induction failure to investigate whether observed survival improvements were due to better front-line antileukemia therapy, better supportive care leading to a decrease in non–leukemia-related death, or both. Five to six times as many deaths occurred following relapse/disease progression compared with toxicity (Table 2). Although the cumulative incidence of deaths related to toxicity is relatively low at approximately 2%, it accounted for a higher percentage of overall deaths as the rate of death from leukemia decreases and was a particular problem among infants. Prevention of treatment-related deaths must be a critical component of efforts to improve childhood ALL survival.

Ten-year survival was 3% to 4% lower than 5-year survival in 1990-1999, when 84% of deaths occurred within 5 years, and only 1% occurred more than 10 years following diagnosis (Appendix Tables A2 to A4). Given this lower 10-year survival rate, the death rates observed in the 2000-2005 era (Appendix Tables A5 and A6), and the shape of the survival curves (Fig 1), we believe that it is extremely unlikely that there will be a significant increase in deaths beyond 5 years for patients diagnosed in 2000-2005, and we anticipate significant improvements in 10-year survival. We anticipate that the 10-year survival rate for children treated on COG ALL trials in 2006-2010 will approach or exceed 90%. The trend from 1990 to 2005 predicts an absolute 2% to 3% increment in survival during each 5-year era. More importantly, randomized COG ALL clinical trials conducted between 1995 and 2005 established superior treatment regimens that then became the baseline therapy for COG trials conducted in 2006 to 2010.[4,5,14,15]

This report underscores the remarkable improvements in the outcomes for childhood ALL since Farber et al[48] first described temporary remissions in 1948. The ongoing discovery of important biologic subsets of ALL[36,38-40,46] will further refine risk stratification and facilitate the combination of molecularly targeted therapies with chemotherapy. As proof of principle, addition of imatinib to chemotherapy resulted in a dramatic increase in survival for pediatric Philadelphia chromosome–positive ALL.[49] As these changes occur, it will remain essential to closely assess the survival for the majority of US children, adolescents, and young adults with ALL who are treated on COG clinical trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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