

Children, Adolescents, and Young Adults With Leukemia: The Empty Half of the Glass Is Growing

TO THE EDITOR: On the basis of survival trends in the acute lymphoblastic leukemia (ALL) trials conducted by the Children's Oncology Group (COG) between 1990 and 2005, Hunger et al¹ predict the 10-year survival of children with ALL entered onto COG trials between 2006 and 2010 will approach or exceed 90%. They also "believe that it is extremely unlikely that there will be a significant increase in deaths beyond 5 years for patients diagnosed in 2000-2005."^{1(p1668)} They chose to compare their results with data from the original nine geographical regions of SEER (SEER9), a 9.5% sample of the United States, in concluding that the 5-year COG survival rate was 3.9% higher than the national average for patients younger than age 15 years and 13.4% higher for 15- to 19-year-olds. The focus of their discussion was on how to help "US children, adolescents, and young adults with ALL who are treated on COG clinical trials"^{1(p1668)} and not expected to survive.¹

What about patients not treated on COG protocols? Figure 1 compares the death rate after diagnosis of ALL between 2000 and 2005 for COG enrollees age 0 to 21 years derived from Figure 1 of the report by Hunger et al¹ (solid gold line) with the data from 18 geographical regions (SEER18)² released on April 15, 2012 for 28.7% of the US population for patients age 0 to 19 years (shaded gray line). The dotted blue line represents an extrapolated cohort of US patients younger than age 20 years who, deducing from the COG and SEER18 curves, were not enrolled onto COG studies. Not only has the death rate among those not enrolled been more than twice that of COG enrollees, exceeding 25% by 8 years, but the rate of increase after 5 years from diagnosis in the non-COG cohort appears to be accelerating instead of slowing. Moreover, at least 9,000 American patients younger than age 20 years, representing approximately 60% of all persons diagnosed with ALL in the age group, were not enrolled onto COG trials between 2000 and 2005. This number includes those who were enrolled onto clinical trials elsewhere, such as the St. Jude Children's Research Hospital and the Dana-Farber Cancer Institute Consortium, and who, if removed, would render the results for the rest of the non-COG patients in our country even worse.

Also ominous is the trend in the proportion of patients with ALL not treated on active COG protocols. From the data in the report by Hunger et al,¹ the average annual accrual to COG ALL studies of patients younger than age 21 years decreased from 1,461 between 1990 and 1994 to 1,434 between 1995 and 1999 to 1,192 between 2000 and 2005. On the basis of the US population in the age range and era,³ the corresponding estimated proportion of patients on COG ALL trials decreased from 73% to 61% to 47%.

The report¹ confirms that adolescents and young adults (AYAs) on COG trials have experienced an increase in survival, as others have reported.⁴ Nonetheless, the 5-year death rate in the most recent COG cohort was 25% for 15- to 19-year-olds. For 10- to 18-year-olds enrolled onto St. Jude Children's ALL trials, the 5-year death rate was 28.9%, 23.8%, 26.9%, and 31.2% in successive studies between 1984 and 1999.⁵

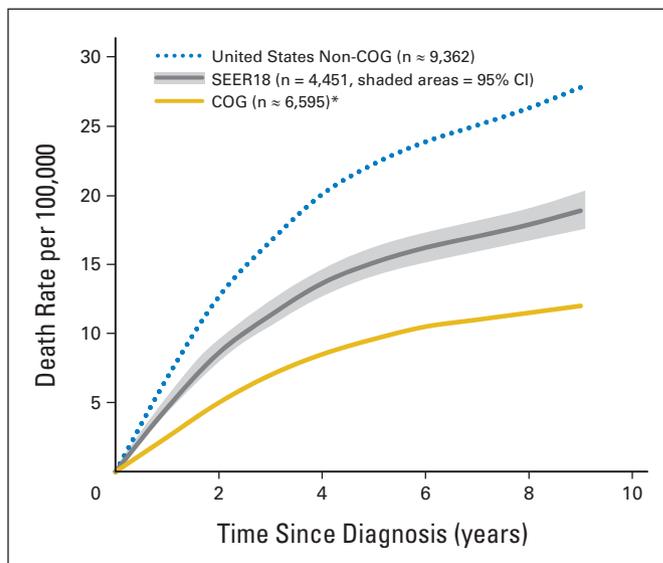


Fig 1. Annual death rate resulting from acute lymphoblastic leukemia in the United States between 2000 and 2005 among Children's Oncology Group (COG) patients younger than age 22 years (solid gold line), SEER18 patients younger than age 20 years (shaded gray line), and by extrapolation United States patients not on COG trials younger than age 20 years (dotted blue line). (*)Number of COG patients treated in the United States. SEER18, data from 18 geographical regions.

Thus the glass half full/half empty analogy is applicable here, with a clear challenge remaining to deliver the progress achieved by COG to the rest of the United States for patients not enrolled onto active clinical trials, particularly AYAs, who experience death rates of two to three times that reported by the authors¹ and death rates progressively diverging from the cooperative group experience. In Los Angeles County, AYAs with cancer who were not treated at National Cancer Institute–designated centers between 1998 and 2008 had a statistically significantly worse 5-year survival than those who were.⁶ The challenge is not limited to AYAs, however, given that children not seen at COG centers with a childhood cancer also do not do as well.⁷

Hunger et al¹ state that optimal treatment for an older adolescent with ALL is referral to a pediatric center and enrollment onto a pediatric cooperative group trial. Not mentioned is referral to an adult treatment center that is participating in a clinical trial for these young adults. The three major adult cooperative groups in the United States are currently conducting a clinical trial (C10403; ClinicalTrials.gov identifier NCT00558519) using a COG regimen to treat patients up to the age of 39.^{8,9} We would also like to highlight the recently released guidelines from the National Comprehensive Cancer Network for ALL¹⁰ and for AYA patients with cancer.¹¹ The guidelines address AYAs with cancer in general and those with ALL specifically and emphasize more explicitly than previously published guidelines the importance of clinical trials in treating the age group. A first step in both guidelines is to consider clinical trials and referral to a cancer center if necessary to access available trials.

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Reply to A. Bleyer et al

Bleyer et al¹ commented on our recently published article.² Consistent with the predictions in our report, recent updates show continued improvements in outcome over time for children, adolescents, and young adults enrolled in Children's Oncology Group (COG) acute lymphoblastic leukemia (ALL) clinical trials. The 5-year overall survival (OS) for 6,662 patients enrolled between 2006 and 2009 is 92.3% (SE 0.7%), which is significantly better than the 5-year OS of the 2000-2005 cohort we reported (90.4%, SE 0.5%; $P = .0015$). We agree completely with Bleyer et al that it is important to encourage the enrollment of children, adolescents, and young adults with ALL onto clinical trials; we share their concerns regarding the outcomes of patients, particularly older adolescents, not enrolled onto clinical trials.

With respect to whether there has been a downward trend in the proportion of US patients with ALL enrolled onto COG ALL trials, it is important to note that whether a patient is enrolled onto a clinical trial depends on several factors, one of which is the availability of an open clinical trial at the time the patient is diagnosed. During the 2000-2005 era, the COG was formed through the merger of four previously existing pediatric oncology cooperative groups, including the Children's Cancer Group (chaired at that time by Bleyer) and the Pediatric Oncology Group. During this time, the legacy Children's Cancer Group and Pediatric Oncology Group ALL trials were still active as

new COG protocols were being planned. Thus although the formation of COG led to a remarkable advance in the investigation of new treatments for childhood cancer, it created unavoidable gaps in clinical trial availability contributing to the lower estimated proportion of children and adolescents younger than age 21 years enrolled onto COG trials during this era. As noted in our article, we estimate that 68% of US children age 0 to 19.99 years that developed ALL in 2009 enrolled onto a COG ALL trial, including 69% of those age 0 to 14.99 years and 51% of those age 15 to 19.99 years.²

As we commented in our article, the proportion of older US adolescents with ALL enrolled onto COG trials has increased in the past 15 to 20 years. This is a positive trend, given the consistent finding in both the United States and Western Europe that older adolescents with ALL enrolled onto pediatric ALL trials fare better than those enrolled onto adult ALL trials.³⁻⁶ This is borne out further by the substantial differences in outcome for older adolescents that we reported as compared with SEER data from the same eras.^{2,7} We are encouraged by the adoption of pediatric ALL regimens by adult cooperative groups for older adolescents and young adults, an effort in which Stock has been an international leader. Space precluded a detailed discussion of these efforts in our article, but we have commented on them extensively in other settings⁸⁻¹⁰ and have worked closely with the leaders of the US adult cooperative groups to facilitate these efforts.

The outcomes for older adolescents treated on pediatric cooperative group trials are well-established. The reasons that underlie inferior outcomes for patients with ALL of similar age treated on adult cooperative