
To the editor:

Overall survival among older US adults with ALL remains low despite modest improvement since 1980: SEER analysis

Mark B. Geyer,1 Meier Hsu,2 Sean M. Devlin,2 Martin S. Tallman,1 Dan Douer,1 and Jae H. Park1,3

1Leukemia Service, Department of Medicine, 2Department of Epidemiology and Biostatistics, and 3Center for Cell Engineering, Memorial Sloan Kettering Cancer Center, New York, NY

Over the past 4 decades, outcomes have improved dramatically among pediatric patients with acute lymphoblastic leukemia (ALL), with observed cure rates now >80% in developed countries.1 This progress can be attributed, in part, to large cooperative group studies, advances in combination chemotherapy, monitoring of minimal residual disease, and use of tyrosine kinase inhibitors (TKIs) for Philadelphia chromosome–positive (Ph+) ALL. Recent series have reported excellent outcomes among adolescents and younger adults with ALL who have been treated with pediatric-inspired regimens.2-4 Despite these advances, 5-year overall survival (OS) remains dismal (~20%) among adults age ≥60 years treated at academic centers and on multi-institutional clinical trials by using established first-line regimens.5,6 European population-based analyses have similarly revealed suboptimal outcomes in this population.7-10 Emerging novel agents provide substantial antileukemic effect with manageable toxicity and may represent attractive therapeutic strategies for older patients with ALL, either as components of initial therapy or as treatment at relapse.11-15 There remains a paucity of data reflecting clinical outcomes in older US adults with ALL, particularly outside clinical trials, which provides historical context for evaluating novel approaches. Therefore, we used the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database to describe secular trends of median OS and long-term clinical outcome over the past 4 decades in US adults age ≥60 years with ALL.

We identified 12,891 patients with ALL from SEER-9 registries by using the International Classification of Diseases for Oncology, third revision (ICD-O-3) codes (http://seer.cancer.gov/siterecode/icdo3.dwhome/index.html). Of 1707 patients age ≥60 years diagnosed in 1980 or later, 1675 had known survival time and were included for analysis of characteristics associated with OS. OS was defined as months from diagnosis until death or study cutoff (December 31, 2012).
Patients surviving <1 month from diagnosis are recorded in the SEER database as surviving 0 months. Median survival and 95% confidence intervals (95% CIs) were estimated by using Kaplan-Meier methods. Three study time periods were predetermined by year of diagnosis (1980-1989, 1990-1999, 2000-2011). Demographic characteristics and county attributes were evaluated for association with OS by using Cox regression. Significant factors ($P < .05$) in univariable analysis were selected for multivariable analysis. Statistical analyses were performed by using SAS 9.4 (SAS Institute, Cary, NC).

Among 1675 adults diagnosed with ALL at age ≥60 years between 1980 and 2011 with known OS reported to SEER registries, there were 1517 deaths. Median OS was 4 months (95% CI, 3-5 months). Three-year OS was 12.8% (95% CI, 11.2%-14.5%), with median follow-up of 26 months (range, 0-286 months) among survivors. Age at diagnosis, time period of diagnosis, known history of cancer preceding ALL diagnosis, and SEER registry region were associated with OS (supplemental Table 1, available on the Blood Web site). Adults age 60 to 64 years achieved 3-year OS of 24% and median OS of 9 months;

### Table 1. Multivariable Cox regression model for association with OS

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median OS (mo)</td>
<td>95% CI</td>
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<tr>
<td>Age at diagnosis, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td>9</td>
<td>8-12</td>
</tr>
<tr>
<td>65-69</td>
<td>7</td>
<td>6-9</td>
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<tr>
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<tr>
<td>85+</td>
<td>0</td>
<td>0-1</td>
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<tr>
<td>Diagnosis year</td>
<td></td>
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</tr>
<tr>
<td>1980-1989</td>
<td>3</td>
<td>2-4</td>
</tr>
<tr>
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<td>2000-2011</td>
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<td>5-7</td>
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<tr>
<td>Prior cancer history</td>
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</tr>
<tr>
<td>No†</td>
<td>4</td>
<td>3-5</td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>2-4</td>
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<tr>
<td>Region‡</td>
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</tr>
<tr>
<td>East</td>
<td>6</td>
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</tr>
<tr>
<td>Northern Plains</td>
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<td>2-4</td>
</tr>
<tr>
<td>Pacific Coast</td>
<td>4</td>
<td>3-5</td>
</tr>
<tr>
<td>Southwest</td>
<td>4</td>
<td>2-7</td>
</tr>
</tbody>
</table>

HR, hazard ratio.

*Patients with unknown classification for any of the included variables were excluded from the multivariable survival analysis.

†Patients in whom ALL was the only malignancy diagnosed, or the first malignancy of ≥2 malignancies were identified as having “no prior cancer history” at the time of diagnosis of ALL.

‡East: Atlanta, GA, and Connecticut; Northern Plains: Detroit, MI, and Iowa; Pacific Coast: San Francisco, CA, Hawaii, and Seattle, WA; Southwest: New Mexico and Utah.
those age ≥75 years at diagnosis exhibited 3-year OS of <10% and median OS of ≤3 months. Patients diagnosed from 2000 to 2011 (vs pre-1990) had superior median OS (6 vs 3 months) and 3-year OS (16% vs 10%) (Figure 1). In multivariable analysis (Table 1), OS decreased significantly in all older age groups (vs adults age 60-64 years; P < .001). Patients diagnosed from 2000 to 2011 (vs pre-1990) had a 20% lower risk of mortality (hazard ratio, 0.80; 95% CI, 0.71-0.91; P < .001). In addition, patients reported to SEER registries in the Northern Plains (vs the East) had increased risk of mortality (hazard ratio, 1.21; 95% CI, 1.05-1.39; P = .01).

Despite modest improvement in median OS among adults age ≥60 years with ALL treated from 2000 to 2011 vs pre-1990, possibly reflecting improvements in supportive care (myeloid growth factors, antiemetics) and TKI therapy for Ph+ ALL, rates of 3-year OS remain decidedly poor. This study has several limitations, including lack of data on individual patients’ disease characteristics and treatment. Nonetheless, this analysis reveals several significant broad trends. Increased risk of mortality was observed with increasing age, even after controlling for other factors. Region of diagnosis was also associated with small but significant differences in OS. Although reasons underlying this finding are unclear, median household income varied by region and was higher in Eastern/Pacific Coast vs Southwest/Northern Plains regions. Availability of centers with expertise in ALL management may also vary by region. A previous population-based study using SEER data reported improved survival among adults age <60 years who had ALL in 1980-1984 vs 2000-2004.16 A Dutch population-based analysis similarly noted improved outcomes in 2007-2012 vs 1989-1994 among adults with ALL age <70 years, with a 5-year relative survival rate of 22% among those 60 to 69 years and 5% among those age ≥70 years in 2007-2012.7 Other recent European registry studies have also noted 3-year OS ≤15% to 20% among adults with ALL age 60 to 65 years or older.8-10 This study describes a greater number of patients age ≥60 years, confirms that OS has improved modestly (albeit significantly) in older adults since 1980, and is strengthened by multivariable analysis as noted above.

Several causes likely contribute to the poor outcomes observed, even among medically fit adults with ALL age ≥60 years, including a greater proportion of patients with Ph+ ALL, increased rates of induction failure, and decreased tolerance of cytotoxic therapy and prolonged myelosuppression. In 1 report of 197 patients treated per CALGB 8811, 3-year OS was only 17% among patients age ≥60 years (n = 18) vs 69% among patients age 16 to 30 years and 39% among those age 30 to 59 years.17 Among patients at MD Anderson Cancer Center treated with hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyper-CVAD) regimen, 5-year OS was 20% among patients age ≥60 years (n = 122) vs 48% in younger patients receiving hyper-CVAD vs 9% among patients age ≥60 years receiving earlier VAD (vincristine, doxorubicin, and dexamethasone) -based regimens. Patients age ≥60 years experienced significantly greater rates of induction failure and treatment-related mortality, the latter largely attributable to infection.5 Analysis of 100 adults age 55 to 64 years treated per Medical Research Council UKALL XII/E COG 2993 similarly reported decreased likelihood of achieving complete response (CR) compared with patients age 14 to 54 years (73% vs 93%), increased incidence of infections during induction chemotherapy (67% vs 45%), and more frequent omissions, delays, or dose reductions of planned therapy; asparaginase was the most commonly omitted agent. Patients age 55 to 64 years (vs 14-54 years) experienced inferior 5-year event-free survival (19% vs 37%) and 5-year OS (21% vs 41%).6 Challenges observed in adapting pediatric-inspired approaches to older adults include optimizing use of asparaginase, corticosteroids, and vincristine to balance efficacy and tolerability. Several pediatric-inspired adult ALL protocols have excluded older patients entirely.2,3,18

Advances in TKI therapy have improved outcomes among patients with Ph+ ALL, comprising >40% of older adults with B-cell ALL (B-ALL) in some series.19 Several reports have demonstrated high rates of morphologic CR after induction with TKI and corticosteroid therapy alone, with minimal toxicity.20 Incorporation of second- and third-generation TKIs (vs imatinib) into first-line regimens may further improve outcomes, although direct comparisons are lacking.21,22 The European Working Group on Adult ALL recently reported 3-year OS of 41% among patients age ≥55 years with Ph+ ALL treated with low-intensity chemotherapy, dasatinib, and corticosteroids.23 Several new therapies for B-ALL, including blinatumomab and inotuzumab, also seem to be acceptably tolerable in older adults and are associated with high rates and durability of CR compared with historically used salvage chemotherapy regimens.24,25 Investigations of CD19-targeted chimeric antigen receptor T cells also holds promise, although experience in older adults remains decidedly limited.24,25 Investigators from MD Anderson Cancer Center have combined inotuzumab with low-intensity hyper-CVAD (cyclophosphamide and dexamethasone at 50% dose reduction and no anthracycline, called mini-hyper-CVAD) with or without rituximab in 34 adults age ≥60 years with newly diagnosed B-ALL, noting CR or pathologic CR in 97% and 2-year OS of 70%.13 Ongoing clinical trials are additionally investigating blinatumomab in combination with first-line therapy in older adults with B-ALL. The registry data herein underscore the limited gains realized from 1980 to 2011 among older adults with ALL in the United States and may serve as a historical standard by which to evaluate these investigational approaches in this patient population.

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ORCID profiles: M.B.G., 0000-0001-5248-9117.

Correspondence: Jae H. Park, Memorial Sloan Kettering Cancer Center, 1275 York Ave, Box #569, New York, NY 10065; e-mail: parkj6@mskcc.org.

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To the editor:

Monocyte subset analysis accurately distinguishes CMML from MDS and is associated with a favorable MDS prognosis

Chetasi Talati, 1,2 Ling Zhang, 1 Ghada Shaheen, 1 Andrew Kuykendall, 1,2 Markus Ball, 1 Qing Zhang, 1 Jeffrey E. Lancet, 1 Kenneth S. Zuckerman, 1 Alan F. List, 1 Rami Komrokji, 1 Lynn Moscinski, 1 and Eric Padron 1

1Malignant Hematology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; and 2Department of Medicine, University of South Florida, Tampa, FL

The diagnosis of chronic myelomonocytic leukemia (CMML), as defined by the World Health Organization (WHO), requires the persistent presence of peripheral monocytosis (≥1×10^9/L), accounting for ≥10% of the total white blood cell count (WBC).1 However, peripheral monocytosis is not pathognomonic of CMML and can be observed in other hematologic neoplasms and benign reactive conditions. Further, monocytes are now recognized as a mixed cohort of hematologic neoplasms even without considering total monocytosis count, genetic, or cytogenetic data.2 Although these data suggests that monocyte partitioning may serve as a compelling diagnostic marker for this disease, the aforementioned study has been the only report to date describing this observation. Further, given the close genetic and clinical association between myelodysplastic...
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