Original Article

Enrollment on Clinical Trials Does Not Improve Survival for Children With Acute Myeloid Leukemia: A Population-Based Study

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BACKGROUND: It is questionable whether enrollment on clinical trials offers any survival advantage at the population level over standard-of-care treatment. The objectives of this study were to describe the impact of trial enrollment on event-free survival and overall survival in pediatric acute myeloid leukemia (AML) using the Cancer in Young People in Canada (CYP-C) database. **METHODS**: Children were included if they had had AML newly diagnosed between ages birth and 14 years from 2001 to 2012. CYP-C is a national pediatric cancer population-based database that includes all cases of pediatric cancer diagnosed and treated at 1 of the 17 tertiary pediatric oncology centers in Canada. Univariate and Cox proportional hazards models were used to evaluate the impact of initial trial enrollment on survival. **RESULTS:** In total, 397 eligible children with AML were included in the analysis, of whom 94 (23.7%) were enrolled on a clinical trial at initial diagnosis. The most common reason for non-enrollment was that no trial was available. The event-free survival rate at 5 years was 57.8% ± 5.2% for those enrolled versus 54.8% ± 2.9% for those not enrolled (P = .75). The overall survival rate at 5 years was 70.1% ± 4.9% for those enrolled versus 66.3% ± 2.8% for those not enrolled (P = .58). Enrollment on a trial was not associated with improved event-free or overall survival in multiple regression analyses. **CONCLUSIONS:** Enrollment on a clinical trial was not associated with improved survival for children with AML in a population-based cohort. Rationale for trial enrollment should not include the likelihood of benefit compared with non-enrollment. ***Cancer* 2018;124:000-000.** *© 2018 American Cancer Society.*

KEYWORDS: acute myeloid leukemia, Canada, cancer, children, clinical trial enrollment, population-based, survival.

INTRODUCTION

Children with acute myeloid leukemia (AML) who are enrolled on collaborative group clinical trials have experienced remarkable gains in survival over the past 40 years.[1] This improvement has been attributed to many factors, including new therapeutics, improved supportive care, the identification of prognostic factors, and risk stratification.[2] Whether enrollment on a clinical trial improves survival compared with non-enrollment has been questioned in both children and adults with cancer.[3,4] To date, there is little evidence indicating that clinical trials offer a beneficial *trial effect* because of challenges such as the lack of an appropriate control comparison and the possibility of confounding and publication bias.[3]

We recently used the Cancer in Young People in Canada (CYP-C) database, a national pediatric cancer population-based data source, to describe enrollment on clinical trials and the factors associated with non-enrollment. In

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the initial study, we observed that, of more than 9000 children with all cancer types included in the data set, approximately 1 in 4 were enrolled on a clinical trial.[5] Next, we evaluated the impact of enrollment on survival in patients with acute lymphoblastic leukemia (ALL) and observed that, in models that were adjusted for demographic, leukemic, and socioeconomic factors, enrollment on trials was significantly associated with better event-free survival (EFS) (hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.47-0.95; $P = .023$) but not overall survival (OS) (HR, 0.69; 95% CI, 0.44-1.08; $P = .102$).[6] In contrast, 2 retrospective cohort studies at separate institutions examining only children with newly diagnosed ALL reported no difference in EFS among enrolled clinical trial participants compared with nonparticipants.[7,8]

Recently, adult patients with cancer who were enrolled on Southwest Oncology Group (SWOG) clinical trials were compared with non-trial controls from the National Cancer Institute's Surveillance, Epidemiology, and End Results program.[9] Among 21 studies that included over 5000 patients, trial participation was not associated with improved OS in studies of patients who had a good prognosis, but OS was better in 9 of 10 studies of patients who had a poor prognosis; this impact did not persist past 1 year, likely because of trial eligibility criteria that excluded patients with more comorbidities.

Children who have AML have a worse prognosis compared with those who have ALL, and treatment for AML is more intensive, with a greater likelihood of treatment-related mortality. Thus, it is possible that the beneficial trial effect reported in ALL will not be observed in pediatric AML. Given the dearth of literature, especially that examining the association of trial enrollment and outcomes among patients with AML, our primary objective was to determine whether pediatric patients with AML who were enrolled on clinical trials differed from those who were not enrolled with respect to EFS and OS.

MATERIALS AND METHODS

Population of Interest and Sampling Methods

We included children with newly diagnosed AML (International Classification of Diseases for Oncology M codes 9840, 9861, 9867, 9870-9874, 9891, 9895-9897, 9910, 9920, and 9931), ages birth to 14 years at diagnosis, who were diagnosed between January 1, 2001, and December 31, 2012, and were treated at 1 of the 17 pediatric oncology centers in Canada. We excluded patients who had a previous diagnosis of malignancy, those with acute promyelocytic leukemia, and those whose enrollment status was unknown.

Data Source

The data source was CYP-C, which is a population-based registry that includes all children (aged <15 years) who have cancer diagnosed and treated at 1 of the 17 tertiary pediatric oncology centers in Canada. CYP-C collects all pediatric cancers diagnosed since 2001 and follows outcomes for 5 years after diagnosis or an eligible second malignancy. Centers in Canada submit data to CYP-C in 2 ways. For the 5 Ontario centers, data are transferred to CYP-C through the Pediatric Oncology Group of Ontario (POGO) Networked Information System (POGONIS), which is a provincial, population-based registry that predates CYP-C. The 12 non-Ontario centers enter data directly into CYP-C. Elements captured by both databases include the following: demographic variables, including sex, date of birth, postal code, and race; diagnostic details; times to diagnosis and treatment; treatment plan details; and outcomes, such as relapse, second malignancy, and death. All information on treatments received and enrollment on trials is included in both POGONIS and CYP-C.

During the study period, 4 Children's Oncology Group (COG) AML trials were available for enrollment in Canada and incorporated the following experimental agents: AAML03P1 (single-arm gemtuzumab), AAML0431 (no experimental agent), AAML0531 (randomization to gemtuzumab), and AAML1031 (randomization to bortezomib and single-arm sorafenib for patients with a high fms-like tyrosine kinase 3 [*FLT3*]/internal tandem duplication allelic ratio).

A standardized list of reasons for non-enrollment was available only for CYP-C centers and not for POGONIS throughout the study period; therefore, reasons for non-enrollment are presented only for the 12 non-Ontario sites. The reason *no available trial* was defined as situations in which a protocol was not open at the institution for the treatment of AML and may have occurred because no protocol was available or because an available protocol was not open at that institution. The reason *not eligible for any trial* was defined as a situation in which a research ethics board-approved protocol was open and available at the time of patient presentation but he or she did not meet eligibility criteria for that trial.

The CYP-C program achieves high-quality data through multiple approaches. A community of practice composed of each site's data manager was established to maximize data quality through monthly teleconferences

and annual face-to-face training combined with site audits.

Statistical Plan

Postal codes at diagnosis were used to determine distance to the nearest tertiary care pediatric cancer center and area-level socioeconomic status by linking to census data. Full 6-digit postal codes were available for all provinces except British Columbia, for which 3-digit postal codes were available. We used the Statistics Canada Postal Code Conversion File software (version 4J; Statistics Canada, Ottawa, Ontario, Canada) to link the postal code at diagnosis to a 2001 census dissemination area. Dissemination areas are the smallest area unit defined by Statistics Canada and include between 400 and 700 individuals. By using this linkage, we determined income quintiles that were adjusted for household size and regional differences.[10–12]

The factors associated with trial enrollment were identified using descriptive statistics. Potential confounders were examined as follows: 1) demographic features, including age at diagnosis (<1, 1-4, 5-9, and 10-14 years), sex, race, and diagnostic era (<2007 vs ≥2007; the approximate midpoint); 2) leukemia features, including the initial white blood cell (WBC) count (≥50 vs <50 × 10^9/L), AML subtype using the French-American-British classification, and cytogenetic risk group; and 3) socioeconomic factors, including kilometers to the nearest tertiary care pediatric center and neighborhood income quintile. We chose a cutoff WBC count of 50 × 10^9/L based on previous studies.[13,14] Good-risk cytogenetics were defined as inv(16), t(16:16), and t(8:21). Poor-risk cytogenetics were defined as monosomy 5/del(5q), monosomy 7, and an FLT3 allelic ratio >0.4.[15] Patients without either good-risk or poor-risk cytogenetics were considered to have standard-risk cytogenetics.

EFS was defined as the time from diagnosis to relapse or death from any cause, whichever occurred first. Those without an event were censored on the date of last follow-up. OS was defined as the time from diagnosis to death from any cause or the date of last follow-up. Survival was described for those who were and were not enrolled on a therapeutic trial at diagnosis using the Kaplan-Meier method and was compared using the log-rank test.

We evaluated the impact of trial enrollment using univariate and multivariable Cox proportional hazards models, and associations were estimated using hazard ratios (HRs) with associated 95% confidence intervals (CIs). Adjusted models included all demographic, leukemic, and socioeconomic factors separately and then together. Statistical significance was defined as $P < .05$. Statistical analysis was conducted using the SAS statistical software program (version 9.4; SAS Institute, Inc, Cary, NC).

RESULTS

In total, 444 children were identified, of whom 37 had acute promyelocytic leukemia and 10 had unknown enrollment status, thus leaving 397 eligible children in the study cohort. Of these, 175 patients (44.1%) were entered through POGONIS, and 222 (55.9%) were entered directly into the CYP-C database. Among children with AML who were included in the study, 94 (23.7%) were enrolled on a clinical trial at initial diagnosis. Table 1 illustrates the demographics of the study cohort. There were 89 children (22.4%) with an initial WBC count ≥50 × 10^9/L, and most children had standard-risk cytogenetics (80.6%). Baseline characteristics that differed significantly between those enrolled versus those not enrolled were diagnostic era and a high WBC count at diagnosis. Among the 211 children who were diagnosed on or after 2007, 65 (30.8%) were enrolled on a trial compared with 29 of 186 (15.6%) who were diagnosed before 2007 ($P = .0004$).

For the 94 patients who were enrolled on a clinical trial, 72 (76.6%) were enrolled on COG protocols (7 on AAML03P1, 5 on AAML0431, 44 on AAML031, and 16 on AAML1031), and the remainder were others or unknown. Conversely, for the 303 patients who were not enrolled on a trial, 145 (47.9%) were treated according to COG protocols, and the remainder were others or unknown.

Table 2 lists the reasons for non-enrollment at the 12 non-Ontario sites, the most common of which was *no available trial* in 101 of 163 patients (62%). Failure to meet eligibility criteria, physician choice, and patient/parent refusal to participate in the trial were all uncommon. We were not able to demonstrate reasons for non-enrollment stratified by diagnostic era because of small cell sizes. However, among those in whom the reason for non-enrollment was known, the reason *no available trial* was not significantly different by diagnostic era, and *no available trial* was the reason for non-enrollment in 58 of 71 patients (81.7%) before 2007 and I 43 of 62 patients (69.4%) on or after 2007 ($P = .145$).

The EFS rate at 5 years was 57.8% ± 5.2% for those enrolled on trials compared with 54.8% ± 2.9% for those not enrolled ($P = .754$) (Fig. 1). The OS rate at 5 years was

TABLE 1. Demographics of the Study Population With Acute Myeloid Leukemia

Variable	No. of Patients (%)				
	Total, N = 397	Enrolled, N = 94	Not Enrolled, N = 303	Enrolled, %	P[a]
Demographic features					
Age at diagnosis, y					.857
<1	55 (13.9)	11 (11.7)	44 (14.5)	20.0	
1-4	134 (33.8)	33 (35.1)	101 (33.3)	24.6	
5-9	94 (23.7)	21 (22.3)	73 (24.1)	22.3	
10-14	114 (28.7)	29 (30.9)	85 (28.1)	25.4	
Sex					
Male	194 (48.9)	49 (52.1)	145 (47.9)	25.3	.469
Female	203 (51.1)	45 (47.9)	158 (52.2)	22.2	
Race					.209
White	256 (64.5)	70 (74.5)	186 (61.4)	27.3	
Asian	45 (11.3)	9 (9.6)	36 (11.9)	20.0	
Arab/West Asian	15 (3.8)	3 (3.2)	12 (4.0)	20.0	
Aboriginal	12 (3.0)	1 (1.1)	11 (3.6)	8.3	
Black	12 (3.0)	0 (0.0)	12 (4.0)	0.0	
Latin American	4 (1.0)	1 (1.1)	3 (1.0)	25.0	
Other	6 (1.5)	0 (0.0)	6 (2.0)	0.0	
Unknown	47 (11.8)	10 (10.6)	37 (12.2)	21.3	
Diagnostic era					.0004
<2007	186 (46.9)	29 (30.9)	157 (51.8)	15.6	
≥2007	211 (53.1)	65 (69.1)	146 (48.2)	30.8	
Leukemia features					
Initial WBC count ≥50 × 10^9/L	89 (22.4)	30 (31.9)	59 (19.5)	33.7	
French-American-British classification					.401
M0	33 (8.3)	5 (5.3)	28 (9.2)	15.2	
M1	90 (22.7)	20 (21.3)	68 (22.4)	22.2	
M2	(7.3)	10 (10.6)	19 (6.3)	34.5	
M4	55 (13.9)	14 (14.9)	41 (13.5)	25.5	
M5	75 (18.9)	20 (21.3)	55 (18.2)	26.7	
M6	6 (1.5)	0 (0.0)	6 (2.0)	0.0	
M7	45 (11.3)	12 (12.8)	33 (10.9)	26.7	
AML not otherwise specified	64 (16.1)	11 (11.7)	53 (17.5)	17.2	
Cytogenetic risk group					.311
Good	62 (15.6)	10 (10.6)	52 (17.2)	16.1	
Standard	320 (80.6)	80 (85.1)	240 (79.2)	25.0	
Poor	15 (3.8)	4 (4.3)	11 (3.6)	26.7	
Socioeconomic factors					
Distance to nearest pediatric oncology center [IQR], km	29.8 [12.0-132.6]	31.0 [10.8-89.9]	29.8 [12.1-136.1]		.562
Income quintile					.98
Missing	11	2	9		
1, Lowest	63 (16.3)	14 (15.2)	49 (16.7)	22.2	
2	85 (22.0)	21 (22.8)	64 (21.8)	24.7	
3	73 (18.9)	18 (19.6)	55 (18.7)	24.7	
4	87 (22.5)	22 (23.9)	65 (22.1)	25.3	
5, Highest	78 (20.2)	17 (18.5)	61 (20.7)	21.8	

Abbreviations: AML, acute myeloid leukemia; IQR, interquartile range; km, kilometer; WBC, white blood cell.

[a] *P* values were determined using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

70.1% ± 4.9% for those enrolled compared with 66.3% ± 2.8% for those not enrolled ($P = .579$) (Fig. 2). For those enrolled versus not enrolled, EFS at 1 year was 70.2% ± 4.7% versus 70.6% ± 2.6%, and OS at 1 year was 86.2% ± 3.6% versus 84.2% ± 2.1%, respectively. The effect of enrollment in the univariate Cox proportional hazards models was an HR of 0.95 (95% CI, 0.66-1.35) for EFS and an HR of 0.89 (95% CI, 0.58-1.35) for OS.

Table 3 lists the factors associated with EFS and OS in univariate analysis. An initial WBC count ≥50 × 10^9/L and age <1 year at diagnosis were associated with significantly worse EFS and OS. Aboriginal ethnicity was

TABLE 2. Reasons for Non-enrollment on Trials in 12 Non-Ontario Institutions, N = 163[a]

Reason for Non-enrollment	Total No. of Patients	Percentage
No available trial	101	62.0
Not eligible for any trial	8	4.9
Physician choice or language barrier, trial not offered[b]	6	3.7
Refused to participate in trial	11	6.7
Other	7	4.3
Unknown	30	18.4

[a]Data from Ontario institutions are not represented, because the Pediatric Oncology Group of Ontario Networked Information System (POGONIS) does not collect reasons for non-enrollment using a standardized list of reasons during the entire study period in their database.
[b]These categories were combined because of small cell sizes

associated with worse OS, but not EFS. The factors associated with better survival were treatment before 2007 (EFS only) and good-risk cytogenetics (EFS and OS). In all adjusted models for demographic, leukemic, and socioeconomic factors, enrollment on trials was never significantly associated with EFS or OS (Table 4).

DISCUSSION

In this population-based analysis of pediatric AML, which is a relatively poor-prognosis cancer, we observed that enrollment on trials was not associated with better EFS or OS. Only one-quarter of patients enrolled in a clinical trial at diagnosis, and a lack of trial availability was the primary reason for non-enrollment. These findings challenge the widespread belief that enrollment on trials offers improved outcomes to patients.

Our results are in contrast to our own study in ALL, in which enrollment on trials was independently associated with improved EFS, but not OS.[6] Patients with ALL have a better prognosis, less intensive treatment, lower relapse rates, and fewer treatment-related deaths, factors that may have led to a different finding in ALL versus AML. However, 2 independent, retrospective cohort studies in pediatric ALL, 1 of which examined trials in the current treatment era,[7,8] reported no difference in EFS because of trial enrollment. In contrast, patients with AML undergo shorter but more intensive myelosuppressive therapy and often require prolonged inpatient hospitalization until neutrophil count recovery. If a positive trial effect is caused in part by supportive care and close monitoring (patient assessments and laboratory tests), then the routine hospitalization of all patients with AML may play a role in negating any benefit of enrollment. Alternatively, patients who have diseases with a poorer prognosis, such as AML, may stand to derive more benefit from clinical trials.

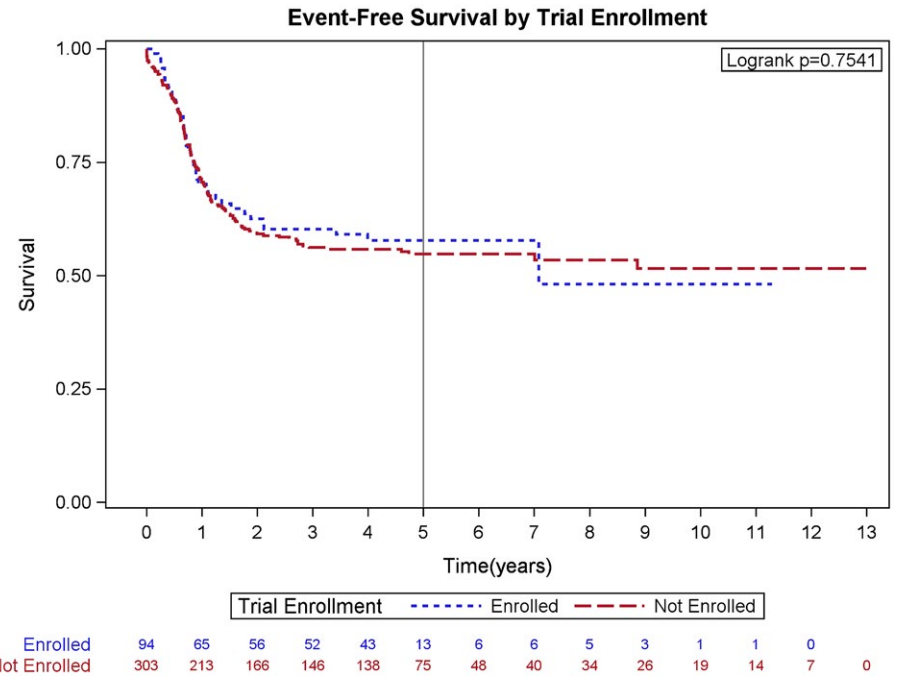

Figure 1. Event-free survival is illustrated according to enrollment status.

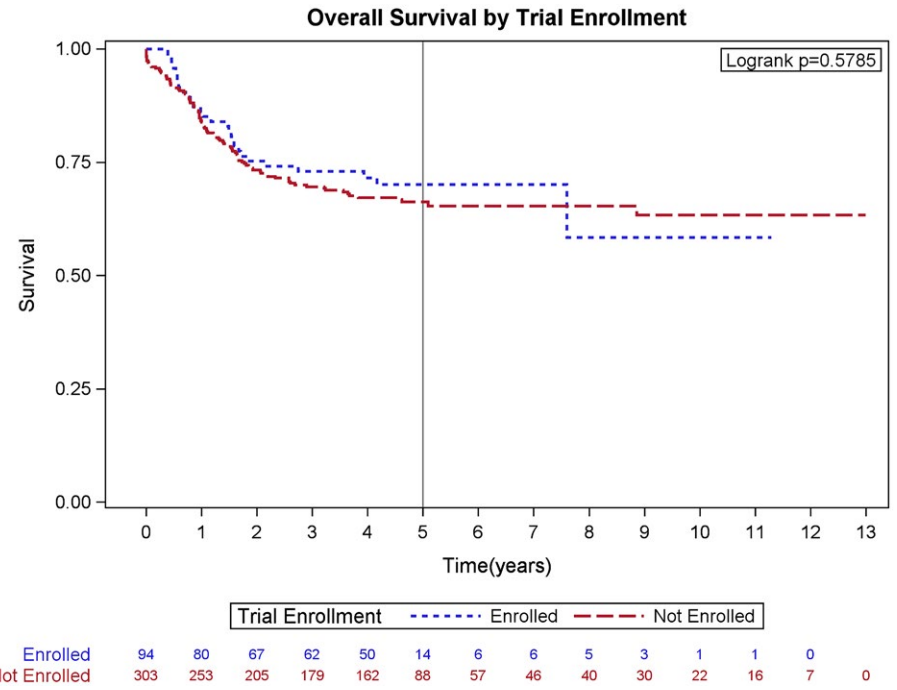

Figure 2. Overall survival is illustrated according to enrollment status.

A large review of adults who received treatment on Southwest Oncology Group national clinical trials indicated that a benefit of enrollment was prominent in 9 of 10 poor-prognosis cancers, 2 of which included AML.[9] However, the benefit in improved OS lasted only 1 year, unlike our study, in which 1-year outcomes were similar between those enrolled versus those not enrolled. It is possible that trial differences are more pronounced in adults versus children, because most children are routinely treated at a tertiary care center and are much less likely to have comorbidities at diagnosis compared with adults. Factors such as hospital experience and supportive care might nullify the beneficial effect of trial enrollment, especially in pediatric AML. Reasons why enrollment on trials does not improve outcomes in AML also may be related to the lack of efficacy of many tested agents and additional toxicity added by the agent under consideration. We recently observed that trial participation may be associated with more infectious toxicity in children with AML.[16]

Lack of trial availability was the most common reason for non-enrollment in our study, occurring in 62% of patients. The majority of Canadian pediatric oncology centers belong to the COG, and, during the study period, 4 COG trials were open in Canada: AAML03P1 (active January 2004 to November 2005), AAML0431 (active March 2007 to August 2010), AAML0531 (active August 2006 to June 2010), and AAML1031 (active June 2011 to July 2017). After COG activation, all trials must obtain Health Canada approval and institutional research ethics board approval, thus leading to variability in when trials are available at each center. Trial enrollment was higher after 2007, which may have been related to multiple factors, although lack of trial availability was not significantly different by era.

Similar to previous studies in both Canada and the United States, we also observed lower survival among those of Aboriginal races.[17,18] It is speculated that health disparities among the Aboriginal population may be attributable to access barriers to health care and poor adherence to therapy, although the results from 1 Canadian study did not support these mechanisms, raising the potential that biology may contribute to poorer outcomes.[17]

Despite these findings, the development of national and international collaborative groups within pediatric oncology over the past one-half century and the inclusion of patients on clinical trials have unquestionably led to incremental gains in survival for multiple cancer types.[1,19] Hundreds of thousands of patients have benefitted from the advancements gained in science through the knowledge built on successive clinical trials. Therefore, failure

TABLE 3. Impact of Trial Enrollment on Event-Free and Overall Survival

	Event-Free Survival		Overall Survival	
Variable	HR (95% CI)[a]	*P*	HR (95% CI)[a]	*P*
Enrollment on trial				
Enrolled	0.945 (0.66-1.35)	.754	0.89 (0.58-1.35)	.579
Demographic features				
Age at diagnosis, y				
<1	1.80 (1.14-2.85)	.012	1.71 (1.01-2.89)	.046
1-4	Ref		Ref	
5-9	1.35 (0.90-2.0)	.14	1.17 (0.73-1.88)	.524
10-14	1.22 (0.83-1.80)	.31	1.16 (0.74-1.83)	.517
Sex				
Male	1.03 (0.76-1.38)	.864	0.88 (0.62-1.25)	.476
Race				
White	Ref		Ref	
Asian	0.98 (0.60-1.60)	.942	1.17 (0.69-2.0)	.564
Arab/West Asian	0.82 (0.36-1.87)	.644	0.78 (0.29-2.14)	.632
Aboriginal	1.91 (0.93-3.91)	.079	2.65 (1.28-5.49)	.009
Black	1.64 (0.76-3.52)	.206	1.92 (0.84-4.41)	.122
Latin American	0.90 (0.22-3.64)	.881	NA	
Other	0.74 (0.18-2.98)	.666	0.49 (0.07-3.51)	.476
Unknown	1.31 (0.83-2.1)	.247	1.1 (0.61-1.97)	.769
Diagnostic era				
<2007	0.71 (0.53-0.97)	.03	0.78 (0.55-1.11)	.169
Leukemia features				
Initial WBC count ≥50 × 10^9/L	1.69 (1.22-2.35)	.002	1.66 (1.13-2.43)	.01
Cytogenetic risk group				
Good	0.56 (0.35-0.90)	.016	0.44 (0.24-0.81)	.009
Standard	Ref		Ref	
Poor[b]	0.35 (0.11-1.1)	.072	0.32 (0.08-1.3)	.111
Socioeconomic factors				
Nearest pediatric oncology center, km	1.00 (1.00-1.00)	.203	1.00 (1.00-1.00)	.593
Income quintile				
1, Lowest	Ref		Ref	
2	0.93 (0.59-1.49)	.771	0.91 (0.53-1.57)	.743
3	0.86 (0.53-1.41)	.549	0.92 (0.52-1.61)	.766
4	0.81 (0.50-1.30)	.378	0.74 (0.42-1.29)	.282
5, Highest	0.62 (0.37-1.04)	.07	0.57 (0.31-1.04)	.068

Abbreviations: CI, confidence interval; HR, hazard ratio; `, not applicable (cannot be calculated because there were no events); Ref, reference category; WBC, white blood cell.
[a]HRs were calculated using a univariate Cox proportional hazards model.
[b]Note that only 15 patients (4%) had poor-risk cytogenetics.

to document a survival benefit in pediatric patients with AML does not suggest that clinical trials should not be conducted in this population and, in fact, may even point to the increased importance of trials given the suboptimal survival outcomes in those with this type of cancer.

At the patient level, there also are major psychological advantages to trial participation. Among adult and pediatric patients, the concept of altruism through the opportunity to help future patients and help advance medical science was a prominent motivation for trial enrollment.[20] Future trials are beginning to include other measures of value rather than the conventional endpoints of relapse and survival. These include patient-reported outcomes, such as quality of life, among others.

The strengths of this study are its population-based nature and the careful collection of confounders, including leukemic and socioeconomic factors. Other strengths are the high quality of data and the common health care system, which provides universal health care. However, these results must be interpreted in light of the study's limitations. First, potentially important covariates were not available, such as minimal residual disease. Second, adolescents and young adult patients are not included in the CYP-C registry. This is important, because several

TABLE 4. Impact of Trial Enrollment on Event-Free and Overall Survival in Adjusted Models

	Event-Free Survival		Overall Survival	
Variables Included in Multiple Regression	HR (95% CI)	*P*	HR (95% CI)	*P*
Demographic: Age, sex, ethnicity, era	0.93 (0.64-1.34)	.684	0.89 (0.58-1.38)	.615
Leukemia: Initial white blood count, cytogenetics	0.86 (0.6-1.23)	.398	0.8 (0.52-1.22)	.304
Socioeconomic: Distance and income quintile	1.0 (0.67-1.52)	.955	1.05 (0.66-1.66)	.851
Demographic, leukemia, and socioeconomic factors	0.924 (0.6-1.42)	.721	0.96 (0.59-1.57)	.88

Abbreviations: CI, confidence interval; HR, hazard ratio.

studies have demonstrated that these patients have lower rates of enrollment on clinical trials.[21–23] Third, our cohort consisted of patients who had newly diagnosed AML. It is unknown whether trial enrollment of patients who have relapsed/refractory disease or those enrolled on earlier phase trials (phase 1 or 2) would have a different effect. Fourth, another explanation for the negative findings may include residual confounding or failure to account for unmeasured confounders. Finally, we used a census-derived, area-based measure of family income rather than obtaining these data directly from the family.

The major challenge in studying the effects of trial enrollment is that clinical trials are not static over time but evolve because of advances in treatment, supportive care, and diagnostic procedures. One generation of clinical trials may have a high rate of positive trials, whereas the next may be mostly negative, with some even demonstrating harm. Hence, any given snapshot describing how participation in clinical trials for a specific patient population affects outcome cannot be predictive of how participation in future clinical trials may affect outcome. The second challenge results from the inability to isolate the effect of the actual treatment or intervention (known as *treatment effect*) from external factors. Indeed, if favorable differences are observed in trial participants that cannot be explained by a treatment effect, then efforts should focus on identifying these factors so that optimal practices can be adopted for all patients regardless of clinical trial participation.

In conclusion, enrollment on a clinical trial was not associated with improved survival for children with AML in a population-based cohort. Rationale for trial enrollment should not include the likelihood of benefit compared with non-enrollment.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Tony H. Truong: Analysis and interpretation of data; writing, reviewing, and editing the article; final approval; and accountable for all aspects of the work. **Jason D. Pole:** Conceptualization; data curation; analysis and interpretation of data; writing, reviewing, and editing the article; final approval; and accountable for all aspects of the work. **Randy Barber:** Analysis and interpretation of data; writing, reviewing, and editing the article; final approval, and accountable for all aspects of the work. **David Dix:** Writing–analysis and interpretation of data; writing, reviewing, and editing the article; final approval; and accountable for all aspects of the work. **Ketan P. Kulkarni:** Analysis and interpretation of data; writing, reviewing, and editing the article; final approval; and accountable for all aspects of the work. **Emilie Martineau:** Analysis and interpretation of data; writing, reviewing, and editing the article; final approval; and accountable for all aspects of the work. **Alicia Randall:** Analysis and interpretation of data; writing, reviewing, and editing the article; final approval; and accountable for all aspects of the work. **David Stammers:** Writing–analysis and interpretation of data; writing, reviewing, and editing the article; final approval; and accountable for all aspects of the work. **Caron Strahlendorf:** Writing–analysis and interpretation of data; writing, reviewing, and editing the article; final approval; and accountable for all aspects of the work. **Douglas Strother:** Writing–analysis and interpretation of data; writing, reviewing, and editing the article; final approval; and accountable for all aspects of the work. **Lillian Sung:** Conceptualization; data curation; analysis and interpretation of data; writing, reviewing, and editing the article; final approval; and accountable for all aspects of the work.

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