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Clinical Trial Participation and Time to Treatment Among Adolescents and Young Adults With Cancer: Does Age at Diagnosis or Insurance Make a Difference?

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ABSTRACT

Purpose
Because adolescent and young adult (AYA) patients with cancer have experienced variable improvement in survival over the past two decades, enhancing the quality and timeliness of cancer care in this population has emerged as a priority area. To identify current trends in AYA care, we examined patterns of clinical trial participation, time to treatment, and provider characteristics in a population-based sample of AYA patients with cancer.

Methods
Using the National Cancer Institute Patterns of Care Study, we used multivariate logistic regression to evaluate demographic and provider characteristics associated with clinical trial enrollment and time to treatment among 1,358 AYA patients with cancer (age 15 to 39 years) identified through the Surveillance, Epidemiology, and End Results Program.

Results
In our study, 14% of patients age 15 to 39 years had enrolled onto a clinical trial; participation varied by type of cancer, with the highest participation in those diagnosed with acute lymphoblastic leukemia (37%) and sarcoma (32%). Multivariate analyses demonstrated that uninsured, older patients and those treated by nonpediatric oncologists were less likely to enroll onto clinical trials. Median time from pathologic confirmation to first treatment was 3 days, but this varied by race/ethnicity and cancer site. In multivariate analyses, advanced cancer stage and outpatient treatment alone were associated with longer time from pathologic confirmation to treatment.

Conclusion
Our study identified factors associated with low clinical trial participation in AYA patients with cancer. These findings support the continued need to improve access to clinical trials and innovative treatments for this population, which may ultimately translate into improved survival.

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INTRODUCTION

Improving the quality and timeliness of cancer care for adolescents and young adults (AYAs) has emerged as a priority area, because this group has experienced variable progress in cancer survival over the past two decades.[1-3] More than 70,000 new cancers are diagnosed in patients age 15 to 39 years each year, approximately eight times the number of those diagnosed in children younger than 15 years of age.[1,4] Excluding homicide, suicide, and unintentional injury, cancer is the leading cause of death in the AYA population.[4,5] However, progress in AYA oncology has been hampered because of the underrecognized cancer risk in this group and knowledge about the most effective treatment settings and protocols for this population.[6]

Diagnosis and treatment can be delayed in AYA patients with cancer as a result of ambiguity about appropriate detection and treatment strategies.[6] Most AYA patients with cancer in the United States are currently treated by community-based oncologists rather than in cancer centers and face a lack of robust community oncology infrastructure.[7] These patients too frequently fall into a no man's land between pediatric and adult oncology and may be treated by any number of specialists or general practitioners.[8] AYA patients are presented with unique challenges during this time of treatment and recovery, including underinsurance and a lack of adequate social support as they transition from adolescence to adulthood with a chronic disease.[9] Furthermore, progress in AYA cancer has been constrained by exceedingly low participation by AYA

patients in the relatively few clinical trials available to them, in part because diagnosing physicians seldom refer these patients to trials.[10] Understanding how these diagnostic and demographic issues translate into practice for AYA patients with cancer in the community setting will be important for future research initiatives to reduce disparities in treatment practices and survival.

The 2005 to 2006 report from the AYA Oncology Progress Review Group[1] highlighted the insufficient focus on AYA cancers and suggested new research initiatives for clinical trials and outcomes research. On the basis of this report, the National Cancer Institute (NCI) initiated the dedicated Patterns of Care (POC) study to evaluate treatment practices for this population in the community setting. Using these data, we examined the association of patient and provider factors with clinical trial enrollment and time to treatment.

METHODS

Data and Sampling Methodology

For the NCI POC study, we identified AYA patients with cancer registered in the Surveillance, Epidemiology, and End Results (SEER) program diagnosed in 2006. SEER is a population-based set of cancer registries that maintains information on incident cancer diagnoses and survival for approximately 26% of the US population.[11] The SEER program routinely collects information on cancer stage, initial course of treatment, and patient demographics. However, because SEER data collection is primarily hospital based, therapy administered in outpatient settings may be under-reported. Therefore, each year, the NCI POC study reviews medical records and queries physicians to obtain more complete information on cancer therapies for selected cancers.[12]

For the POC study, SEER patients were stratified by cancer site, age, race/ethnicity, and registry, and a random sample was selected from each stratum. Non-Hispanic blacks, Hispanics, Asians/Pacific Islanders, and American Indians/Alaskan Natives were oversampled to obtain more stable estimates. Institutional review board approval was received as required by the registries. Once sampled, each patient's physician was contacted to verify treatments administered and obtain names of other physicians who treated the patient. Physicians were queried about patient enrollment onto clinical trials and reasons for nonenrollment. Medical records were reviewed to confirm treatment and identify comorbidites. Comorbidity classifications are described in the Appendix (online only). Finally, information about physician specialty and hospital characteristics were recorded.

Patients

For our study, we sampled 1,358 AYA patients age 15 to 39 years at diagnosis with non-Hodgkin's lymphoma (NHL); Hodgkin's lymphoma (HL); acute lymphoblastic leukemia (ALL); germ cell cancer; and osteo-, Ewing, and synovial sarcomas (hereafter referred to as sarcoma; Appendix [online only] lists included morphology codes). Patients were ineligible if they had a history of cancer (other than nonmelanoma skin cancer), were diagnosed simultaneously with a second cancer, or were diagnosed by autopsy or death certificate. Patients with in situ germ cell cancer, sarcoma, or cancer of the CNS were also ineligible.

Outcome Definitions

We asked treating physicians to confirm enrollment onto clinical trials and treatment initiation dates for each patient. The date of pathologic confirmation was based on pathology reports abstracted by SEER registries. We classified patients as enrolled onto clinical trials (yes/no) if any treating physician or medical record identified registration in a treatment protocol for a patient, including confirmation of any enrollment (yes/no) or identification of a specific protocol sponsor and trial number. We additionally calculated time to first therapy as the difference between the date of pathologic confirmation and first date listed for treatment or therapeutic agent administration. Treatment was categorized into five intervals: 0, 1 to 14, 15 to 30, 31 to 60, and more than 60 days.

Statistical Analyses

To assess unadjusted associations between patient and provider characteristics and cancer treatment, we used χ^2 tests for categorical variables and Wilcoxon-Mann-Whitney U tests for differences in medians. We used logistic regression to evaluate associations between patient and provider characteristics and enrollment onto clinical trials. Finally, we used ordinal logistic regression to assess predictors of increased time to treatment initiation. All analyses were performed using SUDAAN (Research Triangle Institute, Research Triangle Park, NC) and were weighted to reflect SEER populations from which data were obtained. All tests of statistical significance were assessed using Wald-type F-statistics. P values were two-sided, with $P < .05$ considered significant.

RESULTS

Clinical Trial Participation

In our study, 14% of AYA patients diagnosed in 2006 enrolled onto a clinical trial (Table 1). Clinical trial participation was most common in patients with ALL (37%) and sarcoma (32%); only 0.3% of patients with germ cell cancer enrolled. For 61% of patients, the reason for nonenrollment in a clinical trial was not reported (data not shown). When identified, the most frequent reason for nonenrollment was that no clinical trial was currently open or available for enrollment (16%), as reported by the treating physician. Although not treated in an open clinical trial, physicians reported 18% of patients with ALL and 9% with sarcoma as treated according to documented protocols (data not shown).

Patients diagnosed between ages 15 and 19 years had significantly higher clinical trial enrollment than those in all older age groups (34% in those age 15 to 19 years *v* 3% in those age 35 to 39 years; $P < .001$; Table 1). Enrollment also varied by race/ethnicity, with 9% of non-Hispanic whites enrolling compared with 11% of non-Hispanic blacks. Clinical trial participation did not vary by level of comorbidities ($P = .32$).

Patients with Medicaid or private insurance had the highest rate of clinical trial enrollment, at 14% and 13%, respectively (Table 1). Enrollment was lowest among HMO enrollees (7%) and the uninsured (3%). Furthermore, patients treated by pediatric oncologists had the highest rates of enrollment at 70% compared with 11% of those treated by hematologists/oncologists ($P < .001$). Clinical trial participation was highest in large hospitals (> 400 beds), at 12%.

Time to Treatment

Median time to treatment for all patients was 3 days, with significant variation seen across patient and provider characteristics (Table 2). Over 92% of patients with germ cell cancer were treated on the day of pathologic confirmation, generally with orchiectomy, because more than 67% were diagnosed with stage I disease. Similarly, more than 90% of patients with ALL were also treated within 2 weeks of diagnosis. Patients with NHL and HL both had longer times from pathologic confirmation to treatment compared with those with other diagnoses. Patients with HL had the longest time between pathologic confirmation and first therapy, with a median time of 21 days. Nearly 9% of these patients were treated more than 60 days after pathologic confirmation. Similarly, 17% of patients with NHL were treated 31 to 60 days after diagnosis, whereas 8% were treated after more than 60 days. Patients with NHL treated after more than 60 days were most commonly diagnosed with diffuse large B-cell or follicular lymphoma.

Table 1. Demographics and Health Provider Characteristics of AYA Patients by Clinical Trial Enrollment

Characteristic	Clinical Trial Enrollment						P
	Yes		No		Unknown		
	No.	Wt %	No.	Wt %	No.	Wt %	
Total	191	14	1,080	79.5	87	6.5	
Cancer type							< .001
NHL	30	6.4	292	84.9	19	8.7	
HL	43	13.2	279	75.6	24	11.2	
ALL	68	37.4	109	57.7	10	4.9	
Germ cell	4	0.3	291	88.7	23	11.0	
Sarcoma	46	32.1	109	61.9	11	6.0	
AJCC stage, 6th edition							< .001
I	13	2.0	335	83.9	29	14.1	
II	44	11.8	234	78.7	15	9.5	
III	20	10.0	140	85.8	8	4.2	
IV	23	11.8	155	78.7	11	9.5	
Unknown/NA	91	27.5	216	65.3	24	7.2	
Age, years							< .001
15-19	107	34.3	167	62.0	9	3.7	
20-24	34	8.8	230	78.8	19	12.4	
25-29	34	3.4	231	90.1	17	6.5	
30-34	18	5.0	226	85.1	24	9.9	
35-39	17	3.7	226	81.6	18	14.7	
Race/ethnicity							< .001
Non-Hispanic white	89	8.9	491	80.5	41	10.6	
Non-Hispanic black	29	11.2	179	82.4	13	6.4	
Hispanic	54	9.7	289	80.7	21	9.6	
Asian/Pacific Islander	18	10.4	110	81.1	11	8.5	
American Indian/Alaskan Native	1	7.1	11	85.8	1	7.1	
Sex							.02
Male	111	8.3	657	82.5	45	9.2	
Female	80	11.9	423	76.7	42	11.4	
No. of comorbidities							.32
0	133	9.4	738	79.8	62	10.8	
1	36	9.5	222	84.3	16	6.2	
≥ 2	22	9.0	120	81.3	9	9.6	
Insurance							< .001
None	6	3.2	122	84.2	1	12.6	
Private	64	13.9	239	73.0	24	13.1	
HMO	73	7.3	483	85.2	28	7.5	
Any Medicaid	41	14.1	199	77.6	23	8.3	
Other/unknown	7	12.7	37	67.3	11	20	
Physician specialty							< .001
Pediatric oncology only	25	70.5	11	29.5	0	0	
Hematology/oncology only	21	11.0	128	82.7	7	6.3	
Pediatric oncology and other	71	43.3	72	54.8	3	1.9	
Hematology/oncology and other	69	6.6	660	84.4	47	9.0	
Other specialty only/unknown	5	2.0	209	85.7	30	12.3	
Treating hospital size, No. of beds							< .001
Outpatient	3	11.5	24	77.6	3	10.9	
< 200	22	5.8	202	82.2	21	12.0	
200-299	36	7.7	189	79.5	18	12.8	
300-399	36	8.6	216	78.8	17	12.6	
≥ 400	91	12.4	438	82.7	26	4.8	
Unknown	3	33.8	9	52.9	2	13.3	
Residency training program							< .001
Yes	159	12.3	713	83.2	40	4.5	
No/unknown	32	5.3	367	77.4	47	17.3	

Abbreviations: AJCC, American Joint Committee on Cancer; ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; HL, Hodgkin's lymphoma; HMO, health maintenance organization; NA, not applicable; NHL, Non-Hodgkin's lymphoma; Wt, weighted.

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Table 2. Demographics and Health Provider Characteristics of AYA Patients by Time to Initial Treatment

Characteristic	No. of Days From Pathologic Confirmation to First Treatment														
			0		1-14		15-30		31-60		> 60		Unknown		
	Median	Range	No.	Wt %	No.	Wt %	No.	Wt %	No.	Wt %	No.	Wt %	No.	Wt %	*P*
Cancer type															NA*
NHL	19	0-759	35	9.3	108	28.1	63	21.1	58	17.8	29	8.0	48	14.9	
HL	21	0-399	15	3.3	99	29.0	102	28.5	81	21.5	28	8.7	21	8.9	
ALL	1	0-58	47	30.2	122	61.0	8	3.5	5	3.0	0	0	5	2.3	
Germ cell	0	0-399	286	92.6	18	4.9	4	0.7	3	1.1	4	0.4	3	0.3	
Sarcoma	13	0-231	36	21.6	54	31.9	33	20.3	21	14.1	12	6.1	10	5.9	
AJCC stage, 6th edition															< .001
I	0	0-377	205	70.1	47	9.0	25	3.8	39	7.3	26	4.0	27	5.8	
II	20	0-399	41	14.5	89	24.4	74	24.3	58	23.9	22	9.0	9	3.9	
III	11	0-127	49	34.0	43	30.1	37	20.5	22	8.4	10	4.8	7	2.3	
IV	15	0-759	21	10.7	70	32.6	38	25.1	33	14.5	8	4.8	19	12.3	
Missing/NA	1	0-227	95	28.7	152	45.9	36	10.9	16	4.8	7	2.1	25	7.6	
Age, years															< .001
15-19	4	0-274	80	31.9	129	39.8	36	11.2	23	8.9	7	5.9	8	2.2	
20-24	3	0-139	91	39.1	78	24.9	49	13.2	36	11.1	10	2.4	19	9.4	
25-29	0	0-399	99	49.9	67	21.4	33	11.6	33	8.5	17	4.7	14	3.7	
30-34	4	0-349	84	40.8	73	18.5	46	16.1	31	13.7	17	6.1	17	4.9	
35-39	3	0-759	65	41.4	54	12.0	46	17.4	45	13.2	22	5.3	29	10.6	
Race/ethnicity															NA*
Non-Hispanic white	3	0-377	199	42.2	181	21.3	106	14.9	76	11.4	22	4.2	37	6.0	
Non-Hispanic black	12	0-399	55	20.7	61	26.4	35	16.5	33	14.9	21	10.7	16	10.7	
Hispanic	0	0-349	115	47.8	113	20.7	52	11.9	40	9.6	18	3.7	26	6.3	
Asian/Pacific Islander	8	0-759	43	32.0	42	27.6	16	13.4	18	12.0	12	8.8	8	6.2	
American Indian/Alaska Native	0	0-35	7	57.1	4	28.6	1	7.1	1	7.1	0	0	0	0	
Sex															< .001
Male	0	0-759	303	52.4	225	16.9	109	11.6	96	9.9	39	3.9	41	5.1	
Female	14	0-399	116	14.9	176	33.9	101	20.2	72	14.3	34	7.0	46	9.6	
No. of comorbidities															.002
0	1	0-759	310	44.7	268	21.6	137	12.9	109	10.4	49	4.2	60	6.2	
1	12	0-200	66	24.9	89	27.4	50	18.2	37	15.3	17	7.5	15	6.7	
≥ 2	0	0-118	43	45.4	44	16.0	23	15.6	22	10.3	7	4.6	12	8.0	
Insurance															< .001
None	0	0-227	49	59.0	29	12.4	16	10.7	16	9.2	11	5.3	8	3.3	
Private	4	0-759	97	35.3	106	29.9	52	14.2	43	9.9	16	6.2	13	4.5	
HMO	2	0-399	182	42.5	162	18.5	95	14.6	71	12.1	30	4.4	44	7.9	
Any Medicaid	4	0-231	77	35.9	84	27.3	42	17.8	33	11.4	13	3.4	14	4.2	
Other	0	0-98	10	47.9	15	23.7	3	3.3	4	10.9	2	4.2	2	10.0	
Unknown	22	0-112	4	20.4	5	10.8	2	7.5	1	19.4	1	12.9	6	29.0	
Physician specialty															NA*
Pediatric oncology only	2	0-35	9	22.7	22	56.8	3	12.4	2	8.2	0	0	0	0	
Hematology/oncology only	11	0-103	36	21.1	61	36.1	23	15.0	23	15.7	5	5.8	8	6.3	
Pediatric oncology and other	8	0-118	26	26.0	83	45.9	20	10.6	11	7.8	4	8.5	2	1.1	
Hematology/oncology and other	16	0-759	198	34.6	214	22.2	151	18.5	118	13.9	52	5.1	43	5.7	
Other specialty only	0	0-349	145	77.0	17	4.1	12	2.9	13	3.4	11	2.8	28	9.9	
Unknown	7	0-141	5	23.4	4	28.7	1	3.2	1	3.2	1	3.2	6	38.3	
Treating hospital size, No. of beds															< .001
Outpatient	14	0-349	5	18.6	8	26.9	7	24.8	1	4.8	2	6.0	7	18.7	
< 200	2	0-399	80	44.2	55	14.7	39	14.3	35	11.8	14	6.9	22	8.1	
200-299	3	0-200	80	40.4	75	27.8	37	11.0	26	10.5	13	3.5	12	6.8	
300-399	1	0-377	85	47.1	84	19.2	40	14.9	33	9.3	13	4.0	16	5.5	
≥ 400	3	0-759	165	38.0	177	24.1	84	14.5	71	13.3	30	4.9	28	5.1	
Unknown	15	0-68	4	27.1	2	11.3	3	32.6	2	9.7	1	4.8	2	14.5	
Residency training program															< .001
Yes	3	0-759	270	39.0	293	22.5	134	14.5	120	14.0	48	5.2	47	4.8	
No/unknown	1	0-399	149	44.5	108	21.3	76	13.7	48	7.5	25	4.3	40	8.8	

Abbreviations: AJCC, American Joint Committee on Cancer; ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; HL, Hodgkin's lymphoma; HMO, health maintenance organization; NA, not applicable; NHL, Non-Hodgkin's lymphoma; Wt, weighted.

*χ^2 test not performed because of small cell sizes.

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Men had higher rates of treatment on the day of pathologic confirmation compared with women (52% *v* 14%; $P < .001$). However, this difference may be the result of the nature of cancers diagnosed for each, with over 93% of germ cell cancers diagnosed in men. When germ cell cancers were excluded, median time to treatment was more comparable at 15 days for women and 17 days for men. Furthermore, variation existed in time to treatment across race/ethnicity. In our study, over 10% of non-Hispanic blacks and 8% of Asians/Pacific Islanders had a 2-month lag between pathologic confirmation and first treatment.

AYA patients with cancer treated by pediatric oncologists alone were more likely to be treated in the first 2 weeks after diagnosis compared with hematologists/oncologists (79% *v* 57%). Additionally, patients treated in larger facilities had shorter times to treatment. However, time to treatment was similar between facilities with and without residency training programs, with median times to treatment of 3 and 1 days, respectively.

Multivariate Analysis

In multivariate analyses, insurance status, patient age, cancer site, and physician specialty were significantly associated with enrollment onto clinical trials (Table 3). Overall, uninsured patients were 25% as likely to enroll onto clinical trials compared with patients enrolled in private fee-for-service insurance plans (odds ratio [OR], 0.25; $P < .001$); however, contrary to reports in previous literature,[13] health maintenance organization and fee-for-service patient enrollment did not significantly differ in multivariate analyses. Furthermore, patients diagnosed with ALL were most likely to enroll onto a clinical trial compared with patients with NHL (OR, 9.09; $P < .001$), followed by those with sarcoma (OR, 4.47; $P < .001$). As patient age increased, likelihood of clinical trial enrollment decreased, with patients age 35 to 39 years at diagnosis least likely to enroll compared with those age 15 to 19 years (OR, 0.32; $P < .001$). Finally, patients treated by pediatric oncologists were more likely to enroll compared with those treated by hematologists/oncologists (OR, 7.39; $P < .001$).

Cancer stage at diagnosis and size of treating facility were associated with longer time to treatment initiation in multivariate analyses (Table 4). Specifically, patients diagnosed with American Joint Committee on Cancer stage III disease had significantly longer time from pathologic confirmation to cancer treatment compared with those with stage I disease (OR, 4.29; $P < .001$). Furthermore, those treated in outpatient facilities were also more likely to have longer time to treatment initiation compared with patients treated in hospitals with fewer than 200 beds (OR, 2.94; $P < .001$). However, patients treated in larger hospitals (200 to 299, 300 to 399, and 400 or more beds) had no longer time to treatment compared with those treated in hospitals with fewer than 200 beds ($P > .05$ for all). These results were consistent when stratified by cancer site, because germ cell cancers are predominately treated with surgery alone (eg, orchietomy).

Comorbidities

Comorbidities varied by age, cancer site, and race (Table 5; $P < .001$ for all). Comorbid conditions increased with age, with 25% of patients age 15 to 19 years presenting with comorbidities compared with 39% of those age 35 to 39 years. The most striking differences included rates of mental health conditions (7% *v* 11%), overweight/obesity (6% *v* 1%), and hypertension (2% *v* 7%) in those age 15 to 19 years compared with those 35 to 39 years of age ($P < .05$ for all).

Table 3. Patient and Provider Characteristics Associated With Clinical Trial Enrollment in AYAs

Characteristic	OR	95% CI
Cancer type		
NHL	Ref	
HL	1.82	0.85 to 3.88
ALL	9.09	3.2 to 25.83
Germ cell	0.06	0.02 to 0.23
Sarcoma	4.47	2.01 to 9.95
AJCC stage, 6th edition		
I	Ref	
II	1.99	0.84 to 4.73
III	2.11	0.82 to 5.45
IV	2.18	0.82 to 5.8
Missing/NA	0.94	0.35 to 2.56
Age, years		
15-19	Ref	
20-24	0.56	0.29 to 1.07
25-29	0.28	0.1 to 0.73
30-34	0.43	0.19 to 0.96
35-39	0.32	0.15 to 0.69
Race/ethnicity		
Non-Hispanic white	Ref	
Non-Hispanic black	0.7	0.34 to 1.43
Hispanic	0.89	0.47 to 1.69
Asian/Pacific Islander	1	0.45 to 2.22
American Indian/Alaska Native	0.63	0.01 to 28.37
Sex		
Male	Ref	
Female	0.78	0.47 to 1.3
Comorbidity score		
0	Ref	
1	0.69	0.36 to 1.34
≥ 2	0.77	0.34 to 1.71
Insurance		
Private	Ref	
HMO	0.69	0.39 to 1.23
Any Medicaid	0.77	0.36 to 1.64
Other	1.1	0.32 to 3.77
None	0.25	0.08 to 0.76
Unknown	0.12	0.01 to 1.66
Physician specialty		
Hematology/oncology only	Ref	
Pediatric oncology only	7.39	2.49 to 21.93
Pediatric oncology and othger	3.69	1.63 to 8.36
Hematology/oncology and other	1.01	0.53 to 1.94
Other/unknown specialty	0.47	0.14 to 1.59
Treating hospital size, No. of beds		
< 200	Ref	
200-299	1.49	0.56 to 3.98
300-399	2.23	0.96 to 5.16
≥ 400	1.9	0.86 to 4.21
Outpatient/physician office	3.01	0.66 to 13.63
Unknown	2.47	0.46 to 13.32
Residency training program		
Yes	Ref	
No/unknown	0.87	0.46 to 1.62

Abbreviations: AJCC, American Joint Committee on Cancer; ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; HL, Hodgkin's lymphoma; HMO, health maintenance organization; NA, not applicable; NHL, Non-Hodgkin's lymphoma; OR, odds ratio; Ref, reference; Wt, weighted.

From 128.125.208.239

Table 4. Patient and Provider Characteristics Associated With Longer Time to Treatment Initiation in AYAs

Characteristic	OR	95% CI
Cancer type		
NHL	Ref	
HL	2.43	1.05 to 5.6
ALL	0.25	0.07 to 0.92
Germ cell	0.01	0 to 0.02
Sarcoma	0.37	0.16 to 0.87
AJCC stage, 6th edition		
I	Ref	
II	1.82	0.7 to 4.82
III	4.29	1.32 to 13.94
IV	1.45	0.62 to 3.42
Missing	1.87	0.64 to 5.47
Age, years		
15-19	Ref	
20-24	2.56	1.01 to 6.53
25-29	0.98	0.46 to 2.11
30-34	2.38	0.98 to 5.75
35-39	1.65	0.72 to 3.82
Race/ethnicity		
Non-Hispanic white	Ref	
Non-Hispanic black	0.92	0.44 to 1.93
Hispanic	0.78	0.43 to 1.41
Asian/Pacific Islander	1.36	0.59 to 3.15
American Indian/Alaska Native	1.04	0.32 to 3.34
Sex		
Male	Ref	
Female	1.28	0.79 to 2.07
Comorbidity score		
0	Ref	
1	1.17	0.6 to 2.26
≥ 2	0.32	0.15 to 0.68
Insurance		
Private	Ref	
HMO	1.14	0.59 to 2.22
Any Medicaid	0.99	0.49 to 1.96
Other	0.71	0.27 to 1.67
None	0.48	0.2 to 1.13
Unknown	1.3	0.29 to 5.91
Physician specialty		
Hematology/oncology only	Ref	
Pediatric oncology only	2.04	0.46 to 9.1
Pediatric oncology and other	1.62	0.63 to 4.14
Hematology/oncology and other	1.56	0.67 to 3.64
Other specialty only	0.41	0.16 to 1.08
Unknown	5.38	0.86 to 33.66
Treating hospital size, No. of beds		
< 200	Ref	
200-299	2.38	0.89 to 6.35
300-399	1.22	0.61 to 2.44
≥ 400	1.49	0.73 to 3.06
Outpatient/physician office	2.94	1.15 to 7.5
Unknown	0.54	0.07 to 3.84
Residency training program		
Yes	Ref	
No/unknown	1.42	0.77 to 2.63

Abbreviations: AJCC, American Joint Committee on Cancer; ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; HL, Hodgkin's lymphoma; HMO, health maintenance organization; NA, not applicable; NHL, Non-Hodgkin's lymphoma; OR, odds ratio; Ref, reference; Wt, weighted.

Comorbidities were most prevalent in patients diagnosed with ALL and NHL, at 40% and 38%, respectively. Finally, non-Hispanic blacks (43%) and American Indians/Alaskan Natives (53%) had the highest rates of comorbidities compared with non-Hispanic whites (31%).

DISCUSSION

In our population-based study of AYA patients with cancer, we found higher rates of cancer trial participation (3% to 34%) than prior studies of this age group (2% to 15%)[14,15] but comparatively lower participation than in pediatric or older adult populations[15] or those treated in children's hospitals.[10] We also demonstrated in the AYA population that uninsured, older patients and those treated by non-pediatric oncologists were less likely to enroll onto clinical trials. Furthermore, we found a shorter time from diagnosis to treatment in patients with low-stage disease or those treated in hospital settings compared with those diagnosed at later stages or treated in outpatient facilities. These results add to the growing body of literature identifying the need to create effective mechanisms for improving access to and participation in clinical trials among AYA patients with cancer.

Our findings are consistent with national estimates identifying steep declines in clinical trial enrollment as patients enter young adulthood.[15] Since 1997, the NCI Cancer Therapy Evaluation Program has collected patient accrual data from all sites conducting NCI-sponsored clinical trials. It estimated that from 1997 to 2003, 10% to 15% of patients diagnosed between age 15 and 19 years participated in clinical trials. However, for patients age 20 to 30 years at diagnosis, clinical trial enrollment declined to 2% of patients, or just 5% of the rate in children and half the rate in adults age 40 to 65 years.[14,15] Although our population-based study of clinical trial enrollment reflects similar patterns of decreasing enrollment by age, we found higher rates of enrollment than these prior estimates, potentially because of the exclusion of less common AYA cancers with lower than average accrual (eg, CNS tumors, sarcomas) and availability of single-year enrollment estimates.[15] However, accrual rates for this population are still unacceptably low, falling well below clinical trial accrual in large, specialized institutions focused on treating younger populations (eg, children's hospitals), despite the higher likelihood of patients in SEER registries to live in urban areas with higher concentrations of these facilities.[10]

Additionally, our findings draw attention to the continued underenrollment of uninsured AYA patients. In a 1999 study of more than 2,300 patients with cancer in NCI-sponsored clinical trials in the southeastern United States, Klabunde et al[16] found self-pay enrollees age 18 years and older were 60% less likely to participate than privately insured patients. More recently, in a 2010 study of 4,600 adult patients from a single institution, Klamerus et al[17] found over 13% of patients with health insurance who were eligible for and willing to participate in a clinical trial were denied therapeutic trial enrollment because of lack of insurance coverage approval for participation. Because routine care costs associated with clinical trials can be substantial, this barrier can present significant challenges to clinical trial enrollment.[17] Consistent with these results, our findings add to the limited data on the disproportionately low enrollment of uninsured AYAs onto clinical cancer trials.[18-20] Considering that uninsurance rates peak during young adulthood,[21] incorporating newly available reimbursement

Table 5. Patient Comorbidities by Age, Cancer Type, and Race/Ethnicity

	Age at Diagnosis (years)										
	15-19		20-24		25-29		30-34		35-39		
Comorbidity	No.	Wt %	No.	Wt %	No.	Wt %	No.	Wt %	No.	Wt %	*P*
Any comorbidity	72	25.7	82	22.8	68	24.3	107	31.8	96	39.9	< .001
Asthma		5.8		6.2		3.8		4.3		3.8	
Cardiovascular		1.7		1		1.9		5.9		2.5	
Cerebral vascular accident		0.2		0.3		0.1		0		0	
Diabetes		0.9		1.6		1.1		4.6		3.1	
Endocrine		0.6		1		4.5		1.4		4	
GI		1.5		2.1		1.9		6.4		2.5	
HIV/AIDS		0.3		0.5		0.1		2.9		6.8	
Hematologic		1		0.3		0.9		1.3		2.6	
Hypertension		2.6		1.6		4.6		7		7.4	
Liver		0.6		2.8		2.5		0.4		2.3	
Life-threatening infection		1.4		0		0		0.1		0	
Mental health		7.3		5.6		6.8		4.8		11.3	
Neurologic		3.1		4.1		4.2		1.4		4.1	
Obesity/overweight		6.3		2.3		2.6		2.9		1.8	
Renal		1.2		0.6		0.3		0.9		2.4	
Rheumatologic/autoimmune		0.2		0.7		0.1		3.5		2	
	Cancer Type										
	NHL		HL		ALL		Germ Cell		Sarcoma		
	No.	Wt %	No.	Wt %	No.	Wt %	No.	Wt %	No.	Wt %	*P*
Any comorbidity	119	38.0	111	33.0	78	40.0	74	20.4	43	25.7	< .001
	Race/Ethnicity										
	Non-Hispanic White		Non-Hispanic Black		Hispanic		Asian/Pacific Islander		American Indian/ Alaska Native		
	No.	Wt %	No.	Wt %	No.	Wt %	No.	Wt %	No.	Wt %	*P*
Any comorbidity	202	31.3	90	43.4	94	20.8	32	23.1	7	53.6	< .001

Abbreviations: ALL, acute lymphoblastic leukemia; HL, Hodgkin's lymphoma; NHL, Non-Hodgkin's lymphoma; Wt, weighted.

and coverage mechanisms for this population after a cancer diagnosis will be important to reduce barriers to clinical trial enrollment.[22]

Our study also points toward potential barriers to efficient treatment initiation. Our results identified advanced stage and outpatient-based care as important contributors to longer time from diagnosis to treatment. Although some cancers require more extensive workup before treatment (eg, computed tomography scans, bone marrow biopsies), leading to longer time from diagnosis to treatment, over 18% of patients treated in outpatient facilities had not begun treatment more than 60 days after diagnosis. Additionally, although stage I germ cell cancers are predominately treated with surgery at diagnosis, we continued to find longer time to treatment initiation in those with high- versus low-stage cancers when each site was examined separately. These findings are consistent with research identifying the multifactorial nature of delayed treatment, which may be driven by a number of patient, provider, and system factors.[23,24] Delays may result from combinations of insurance coverage at diagnosis,[25] patient preferences surrounding treatment,[26] or the necessity to refer patients to specialists for care (eg, ALL). Future research should focus on identifying efficient transitions from diagnosis to treatment, including mechanisms for referral of AYA patients to tertiary care facilities that offer specialized cancer treatment or clinical trial participation (eg, comprehensive cancer centers, children's hospitals, AYA cancer programs).

Although many factors contribute to low clinical trial participation, one obstacle often identified is the lack of clinical trials for a patient's specific disease and stage at diagnosis. This may result from the relative concentration of clinical trials around common malignancies such as ALL and sarcoma, which have higher incidence among younger patients.[7,27] As a result, protocols for these cancers often have less lag time between the end of one trial and initiation of another because of the increased number of patients overall and their ability to reach enrollment targets faster.[7,28,29] Several mechanisms exist to provide information to physicians about available trials; however, future research should identify effective ways to promote physician utilization of these resources.

In addition, ambiguity surrounding standards of care may also result in treatment delays. Lack of evidence-based guidelines specific to the AYA population often results in a decision to treat these patients based on arbitrary age cutoffs,[30,31] such as 18 years of age. Even though treatment practices directed at adults and children can differ substantially, those younger than age 18 or 21 years are often referred to pediatric oncology specialists, who as we demonstrated are associated with higher clinical trial enrollment, whereas older patients are

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referred to medical oncologists.[28] Multiple studies of ALL in North America and Europe have shown AYA patients treated with pediatric-based protocols have better outcomes than AYA patients treated with protocols used for adults older than 18 years of age.[32-38] Currently, the CALGB (Cancer and Leukemia Group B) 10403 study is evaluating whether pediatric-based protocols for patients with newly diagnosed ALL produce similar outcomes when administered by pediatric oncologists compared with hematologists/oncologists.

In response to the lack of available clinical trials for AYA patients with cancer, several approaches have been instituted. In 2000, the Children's Oncology Group started its own AYA committee to establish disease-specific study groups to increase therapeutic and biologic research protocols for this population. Additionally, numerous Children's Oncology Group protocols have extended upper age limits to 30 years for ALL and 50 years for rhabdomyo- and Ewing sarcomas. Furthermore, in June 2009, the NCI and Lance Armstrong Foundation sponsored a workshop to investigate whether the cancer biology in AYA patients diagnosed with breast cancer, colon cancer, and ALL are unique compared with that in other age groups. These initiatives provide promising new opportunities to address issues of effective treatment and clinical trial enrollment in the AYA population.

In summary, our study identifies low cancer trial participation in AYA patients with cancer, particularly among young adults. These findings support the need for improving access to clinical trials in the AYA patient population through continued education of patients and treating physicians, which will translate into better understanding of the biology of AYA cancers and ultimately into improved survival.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

Adolescent and Young Adult Comorbidity Categories With Included Conditions

Comorbidities were abstracted from the hospitalization record for initial cancer treatment (up to 13 conditions). Because no standard comorbidity index currently exists for the adolescent and young adult (AYA) age group, we created a comorbidity index based on the four most relevant indices (Charlson, Elixhauser, Fleming, and Tai) from pediatric and adult populations (Charlson ME, Pompei P, Ales KL, et al: J Chronic Dis 40:373-383, 1987; Elixhauser A, Steiner C, Harris DR, et al: Med Care 36:8-27, 1998; Fleming ST, Rastogi A, Dmitrienko A, et al: Med Care 37:601-614, 1999; Tai D, Dick P, To T, et al: Arch Pediatr Adolesc Med 160:293-299, 2006). Conditions in the AYA comorbidity index had to be chronic and significant (ie, serious and expected to affect treatment or outcomes or create significant health burden). We did not include conditions listed in established indices if they were acute or self-limited conditions (eg, femur fracture, acidosis). Finally, because timing of the comorbidities was not available, we excluded any conditions that could be related to cancer diagnosis or treatment. Conditions were categorized into 16 large groups (cardiovascular, renal, diabetes, and so on) and summed to create a final AYA comorbidity score. Patients could have more than one comorbidity within a group (eg, two mental health comorbidities) that contributed to the total score. All conditions were weighted equally in the final comorbidity index. We provide a list of the 16 comorbidity categories and include conditions for each. Comorbidities were based on actual conditions reported in the AYA cohort and do not necessarily represent an exhaustive list of comorbid conditions that may present in this age group.

1. Cardiovascular. Old myocardial infarction, heart disease, arrhythmias, valvular disorder/undiagnosed murmurs, pulmonary embolism, peripheral vascular disease, congestive heart failure, congenital heart anomalies (eg, ventricular septal defect), coronary occlusive disease, coronary artery disease, atrial thrombus, cardiomyopathy, Wolff-Parkinson-White syndrome, cardiomegaly, angina, deep vein thrombosis, and persistent tachycardia.

2. Respiratory. Asthma, chronic obstructive pulmonary disease, chronic bronchitis, bronchiectasis, granulomatous lungs, and interstitial emphysema.

3. Diabetes mellitus.

4. Endocrine. Thyroid disorder, polycystic ovaries, pituitary disorder, goiter, Grave's disease, Hashimoto thyroiditis, adrenal insufficiency, other unspecified disorders of pancreatic internal secretion, corticoadrenal insufficiency, and hypogonadism.

5. GI. Ulcers/peptic ulcer disease, esophagitis, gastritis, colecystitis, bowel disease, irritable bowel syndrome, GI bleeds, fistulas, stenoses, chronic pancreatitis, habit vomiting, stomach function disorders, dieulafoy lesion, sclerosing mesenteritis, disorder of the peritoneum, rectal and anal disease, not otherwise specified, cholestasis, and obstructive jaundice.

6. Liver. Hepatitis A, B, and C, cirrhosis, and liver necrosis.

7. Hematologic. Sickle cell disease and other hereditary anemias, von Willebrands, idiopathic thrombocytopenic purpura, aplastic anemia, hemophilia A with severe factor VIII deficiency, defibrination syndrome, disseminated intravascular coagulopathy, acquired coagulation factor deficiency, coagulation defect not otherwise specified, and aplastic red cell crisis.

8. HIV/AIDS.

9. Hypertension.

10. Mental health. Paranoid schizophrenia, schizoaffective disorder, bipolar disease, psychosis, autism, Asperger's syndrome, obsessive compulsive syndrome, borderline personality syndrome, depression, anxiety, adjustment disorder, mild/moderate mental retardation, low IQ with low functioning capabilities, other cerebral degeneration, Down syndrome, Turners syndrome, and developmental delay/lack of expected normal development.

11. Neurologic. Migraines, cluster headaches, epilepsy/seizures, cerebral palsy, spina bifida, hemiplegia/paralysis, multiple sclerosis, neurofibromatosis, anoxic encephalopathy, advanced encephalopathy leading to brain death, Charcot-Marie tooth syndrome, herpetic meningoencephalitis, and muscular dystrophy.

12. Obesity/overweight.

13. Renal. End-stage renal disease, renal transplantation, unspecified renal failure, chronic renal disease/failure, nephrotic syndrome, and polycystic renal disease.

14. Rheumatologic/autoimmune diseases. Juvenile rheumatoid arthritis, osteoarthritis, polyarthritis, arthritis, gout, immunoglobulin A deficiency, common variable immunodeficiency, antiphosolipid antibody syndrome, chronic lupus, and rhabdomyolysis.

15. Life-threatening infection. Clostridium difficile colitis.

16. Cerebrovascular disease. intracerebral hemorrhage and cerebral infarction.

Included Morphology Codes

Non-Hodgkin's lymphoma. M-9590-9596, 9670, 9671, 9673, 9675, 9678 to 9680, 9684, 9687, 9689 to 9691, 9695, 9698 to 9702, 9705, 9708, 9709, 9714 to 9719, and 9727 to 9729.

Hodgkin's lymphoma. M-9650-9655, 9659, 9663 to 9665, and 9667.

Acute lymphoblastic leukemia. M-9835-9837.

Germ cell cancer. M-9060-9091 and 9100 to 9102.

Osteo-, Ewing, and synovial sarcomas. M-9040-9044, 9180 to 9187, 9192 to 9195, 9260, and 9365.

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