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Adoption of Pediatric-Inspired Acute Lymphoblastic Leukemia Regimens by Adult Oncologists Treating Adolescents and Young Adults: A Population-Based Study

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Abstract

Background—Studies show superior outcomes for adolescent and young adult (AYA) patients with acute lymphoblastic leukemia (ALL) treated following pediatric versus adult ALL therapeutic regimens. Whether adult oncologists in the United States have adopted this approach to AYA ALL is currently unknown. We sought to provide a population-based description of AYA ALL treatment patterns over the past decade.

Methods—Data on AYAs 15-39 years and diagnosed with ALL during 2004-2014 while living in the Greater Bay Area were obtained from the Greater Bay Area Cancer Registry (GBACR). Treating facilities were designated as pediatric or adult centers; induction treatment regimens were abstracted from registry text data fields.

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Results—Of 304 patients diagnosed in the GBACR catchment region, complete treatment data was available for 229 (75%). Location of care was identified for 296 (97%) patients treated at 31 unique centers. 70% of AYAs received induction therapy at an adult center. All AYAs treated at pediatric centers received pediatric ALL regimens. Among AYAs treated by adult oncologists with complete treatment data, none received a pediatric regimen prior to 2008. From 2008-2012, while the adult intergroup C10403 pediatric-inspired ALL protocol was open to accrual, 31% of AYAs treated by adult oncologists received pediatric regimens. This fell to 21% in 2013-2014. Adult facilities treating ≥2 AYA ALL GBACR patients per year were more likely to administer pediatric regimens than lower volume centers (P= 0.03).

Conclusion—As of 2014, only a minority of AYAs with ALL received pediatric ALL regimens at adult cancer centers.

Introduction

Over the past decade, a large body of research has focused on discrepancies in the treatment approach and survival of adolescents and young adults (AYAs) with acute lymphoblastic leukemia (ALL) treated in the pediatric versus adult setting. A multitude of retrospective analyses from United States (U.S.) and European cooperative groups conclude that, independent of traditional ALL risk factors, AYAs with ALL have markedly superior outcomes when treated by pediatric oncologists following pediatric treatment protocols.[1-5] In general, pediatric ALL regimens are more intensive and more highly regimented than adult regimens, likely contributing to their improved success.[6]

The intriguing findings from the retrospective studies[1-5] led many groups to prospectively consider the feasibility and outcomes of pediatric inspired protocols administered to AYAs with ALL by adult oncologists.[7, 89-13] Recently, preliminary results of U.S. Intergroup study C10403, the largest prospective evaluation of a pediatric treatment approach applied by adult oncologists to AYAs with ALL have been presented.[14] Among 318 AYAs 17-39 years old enrolled from 2007-2012, 2-year event-free survival (EFS) and overall survival (OS) were 66% and 78%, respectively, which was considerably higher than EFS and OS of 34% and 46% of historical controls treated on US adult cooperative group trials for ALL. [14]

With accumulating evidence supporting the notion that AYAs with ALL should be treated according to pediatric-inspired protocols, many potential obstacles in the U.S. exist. While ALL is the most commonly occurring malignancy in children, ALL occurs less commonly in in adults, accounting for only 15% of all leukemia and 0.4% of adult cancer diagnoses in the U.S.[15] A large proportion of AYA ALL is treated in the community, rather than at National Cancer Institute (NCI)-designated Comprehensive Cancer Centers.[16] The pediatric-inspired regimens recommended for AYA ALL include drugs and therapeutic combinations that are not routinely used in adult oncology practice; thus, implementation of pediatric-inspired regimens which require frequent and prolonged outpatient therapy may be daunting for adult oncologists who treat a paucity of patients with ALL each year. As one example, the delivery of asparaginase throughout the treatment period is critical to the success of pediatric ALL regimens, but use of this agent requires familiarity with its potential toxicities.[17]

The seminal finding that more AYAs with ALL may be cured if treated with pediatric-inspired regimens is only meaningful if adult oncologists routinely and successfully adopt and adhere to these treatment protocols. Thus, to understand changes in the utilization of pediatric-inspired ALL regimen over the past decade, we used facility-level data from a population-based cancer registry to describe AYA ALL treatment patterns among pediatric and adult oncologists.

Methods

Data were abstracted from the population-based Greater Bay Area Cancer Registry (GBACR), a part of the California Cancer Registry (CCR) and the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program. The GBACR includes approximately 6.8 million residents of the nine-county Greater Bay Area ([GBA]; Alameda, Contra Costa, Marin, Monterey, San Benito, San Francisco, San Mateo, Santa Clara, Santa Cruz) who receive a cancer diagnosis within the counties, regardless of health insurance status or treating facility. Case selection included all AYAs aged 15-39 years at diagnosis of ALL (*International Classification of Diseases for Oncology*, 3rd edition,[18] codes 9826, 9835, 9836, 9811-9818, 9837 as per SEER site recode for ALL), with diagnosis occurring between 2004 and 2014. Because GBACR data were used for this analysis, only GBA residents are included; residents outside of the GBACR counties but treated in a facility in the GBA region are not included in this analysis. Conversely, a small number of patients diagnosed in the GBA but receiving induction therapy outside of the GBACR were included, as their treatment data was reported to the GBACR.

Patient and tumor characteristics were obtained from the GBACR (routinely collected for the registry via medical record abstraction) including age at diagnosis, sex, race/ethnicity, health insurance status at the time of initial diagnosis or treatment, and a previously developed composite measure of neighborhood socioeconomic status (SES) that incorporates Census block group level data on income, education, housing costs, and employment; patients were assigned to statewide SES quintiles based on their address at time of diagnosis.[19, 20] Year of diagnosis was categorized as 2004-2007, 2008-2012, and 2013-2014, reflecting potentially relevant events in AYA ALL, including the accrual period of C10403 from 2008 through 2012.[14]

We reviewed all available GBACR facility-level reports for each patient. These facility-level reports reflect information reported to the GBACR from each facility, and are normally consolidated to the tumor level when reported to SEER. For each patient diagnosed in the GBA and captured in the GBACR, initial ALL induction chemotherapy regimen was abstracted from a data text field. Treatment regimens included in the analysis were listed by name in the registry (e.g. “C9511”, “hypercvad”, etc.). Individuals with registry treatment text fields that included only therapeutic agents without specific regimen name (e.g. cyclophosphamide, vincristine, doxorubicin, dexamethasone without mention of specific regimen) were designated as unclear (neither adult nor pediatric) and were not coded as a specific regimen. Induction regimens were categorized as either adult or pediatric/pediatric inspired ALL regimens. Adult ALL regimens included hypercvad,[21] U.S. adult cooperative group regimens (C8811,[22] C9511,[23] C19802,[24] E2993,[25] C10701 [NCT01256398], E1910

[NCT02003222]) excluding intergroup C10403,[14] and the Linker regimen.[26] Pediatric/pediatric-inspired regimens included C10403,[14] the Dana-Farber Cancer Institute pediatric-inspired regimen,[11] and any U.S. pediatric cooperative group ALL regimen.

Physicians involved in the care of the patient (attending physician, medical oncologist, radiation oncologist, referring physician, follow-up physician, and up to two additional physicians) are recorded in the registry. The medical license numbers of all physicians listed for each patient were cross-referenced with CCR and GBACR physician databases to obtain the physician's medical specialty. The facility where induction treatment was administered (treatment setting) was designated as either a pediatric or adult setting. Patients receiving induction in a facility that reports to the GBACR as a stand-alone children's facility (cross referenced with a list of Children's Oncology Group pediatric cancer centers[27] and children's hospitals[27] across California) were considered to have been treated in a pediatric setting. Patients receiving induction in a facility that does not treat children were considered to have been treated in an adult setting. Patients treated at institutions that treat both children and adults and do not report cancer cases from their pediatric and adult hospitals separately were identified as treated in a pediatric setting only if the treating physician was a pediatric oncologist. Cases where treatment setting (pediatric versus adult) could not be clarified through this methodology were considered to have unidentifiable treatment setting, and were not included in further analyses. Hospitals were classified by their affiliation with an NCI-designated cancer center, and facility AYA ALL volume during 2004-2014 was calculated based on the number of AYA ALL inductions administered by each facility in our dataset. If more than one facility reported administering chemotherapy, individual records were reviewed to identify the hospital that administered the induction regimen.

Descriptive statistics (frequencies, percentages) characterized baseline patient, hospital, and treatment characteristics by treatment settings and regimens. Differences between pediatric and adult treatment settings and pediatric and adult ALL regimens administered in adult treatment settings were evaluated using Fisher's exact test. Statistical analyses were performed using SAS versions 9.3 and 9.4 (Cary, NC); 2-sided *P*-values of <0.05 were considered statistically significant. This study was approved under the GBACR IRB protocol by the Cancer Prevention Institute of California Institutional Review Board.

Results

Patient Characteristics and Treatment Setting

304 AYAs with ALL diagnosed in the GBA during 2004-2014 were identified (see Figure 1 for cohort diagram). Treatment setting where induction chemotherapy was administered was captured for 296 (97%) patients; eight patients for whom treatment setting could not be discerned were excluded from additional analyses. Treatment occurred in 31 unique facilities. Of these, two were exclusively pediatric facilities and Children's Oncology Group member institutions. An additional eight pediatric facilities that report to the CCR as part of a larger institution were identified by the treating physicians' specialty and practice location. Of these, half were Children's Oncology Group member institutions. The remaining 21 treatment facilities were exclusively considered to be adult facilities, of which 3 are NCI-designated cancer centers.

The majority of AYAs in our study (n=207; 70%) received initial induction therapy in an adult setting (Table 1). AYAs treated in the adult setting were older (P<0.0001) and more likely to be non-Hispanic White (P= 0.02) than AYAs treated in the pediatric setting. Patients treated in an adult setting were less likely to be treated at a facility associated with an NCI-designated cancer center (P= 0.042), and more likely to be treated at low volume AYA ALL centers (P< 0.0001).

Shifts in Treatment Setting over Time

For the youngest AYAs (aged 15-18 years), the majority received therapy in a pediatric setting (93%), with no significant changes in treatment setting over time (Figure 2). Older AYAs (aged 25-39 years) were exclusively treated in adult settings throughout the decade. For AYAs aged 19-24 years, there was a shift towards ALL treatment increasingly being delivered in pediatric, as opposed to adult, centers over time (P< 0.0001).

Treatment Regimens Administered to AYAs in Adult Setting

Complete induction regimen data was available for 229 (75%) of the entire cohort. 89 AYAs were treated in a pediatric setting from 2004-2014, all of whom received pediatric ALL regimens. Most (81%) AYAs received Children's Oncology Group regimens, either as part of clinical trial or as standard of care.

Amongst the 207 AYAs treated in an adult setting, complete induction regimen data was available for 149 (72%); 56 (27%) received treatment that could not be clearly identified as a pediatric or adult ALL regimen, and 2 patients died prior to treatment administration (Figure 1). The treatment regimen was increasingly identifiable over time: 57% treated from 2004-2007,79% treated from 2008-2012, and 81% treated from 2013-2014 had identifiable induction regimen data, respectively.

The majority (79%) received adult ALL regimens from 2004 to 2014, with hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone (Hyper-CVAD) being the most frequent regimen (Table 2). Prior to 2008, no AYA ALL patients treated in the adult setting received a pediatric-inspired ALL regimen. During 2008-2012, while C10403 was open to accrual, 25% of the AYAs treated in the adult setting received a pediatric-inspired ALL protocol, with most receiving the C10403 regimen either on or off protocol. Following closure of C10403, 21% of AYAs treated in the adult setting from 2013 to 2014 received a pediatric-inspired ALL regimen.

Factors Associated with Receipt of a Pediatric ALL Regimen in the Adult Setting

AYAs who received a pediatric ALL regimen in the adult setting were more likely to be diagnosed between 2008 and 2012 (as opposed to 2004-2007 or 2013-2014), to receive induction treatment at an NCI-designated cancer center, and to receive induction treatment at a facility that treated ≥2 AYA ALL patients per year (Table 3). In the adult setting, the distribution of patient-related variables, such as age, race/ethnicity, neighborhood SES, and health insurance status were similar for AYAs who received a pediatric versus adult ALL regimen.

Discussion

AYAs with ALL represent a unique population at a crossroads between pediatric and adult oncology. However, the gap between recommended pediatric versus adult approaches to AYA ALL has narrowed through retrospective and prospective research demonstrating that outcomes for AYAs with ALL are superior when these patients are treated using pediatric-inspired ALL regimens, regardless of the setting in which they are delivered.[1-3, 5, 7-14] Although this message has been disseminated throughout the oncology literature and through clinical guideline summaries and practice recommendations internationally and in the U.S.,[28, 29] our results based on a population-based case series, show that as recently as 2014, only a minority of AYAs with ALL who receive care across a wide variety of adult oncology facilities in Northern California are treated following pediatric ALL regimens.

There are several likely explanations as to why the adoption of pediatric-inspired ALL regimens may be slow within the general adult oncology community in the U.S. As shown by others and supported in our results, unlike pediatric ALL, most adult ALL in the U.S. is not treated in highly specialized, high volume ALL centers.[16] Strikingly, we found that one-third of AYA ALL patients treated in adult settings are cared for at centers that treat one or fewer AYA ALL patients per year. Adult oncologists who rarely treat ALL may be less familiar with literature supporting a pediatric treatment approach for AYA ALL. Furthermore, they may also be less comfortable with the often challenging schedules and drug administration associated with pediatric ALL protocols. In addition, specific pediatric ALL regimen related toxicities may be heightened in the AYA population,[30, 31] such as steroid-induced osteonecrosis, hepatotoxicity and thrombosis related to asparaginase, which, if encountered, may lead to an unwillingness to embark upon these intensive ALL regimens in other AYAs. Additional work is needed to more clearly understand the knowledge gaps and barriers to utilization of pediatric-inspired ALL protocols within the diverse U.S. adult oncology community.

In addition to describing oncologist practice patterns, our work provides a general overview of where AYAs with ALL are receiving care in the U.S. Not surprisingly, AYAs ≤18 years were almost entirely treated at pediatric centers, while AYAs ≥25 years were universally cared for in adult treatment settings. What is perhaps most interesting is to examine the group of AYAs aged 19-24, who are truly at the intersection between teenage years and young adulthood. Our data reveal that this group may be increasingly cared for at pediatric centers, or perhaps within AYA programs housed in pediatric centers. Given the small sample size of these patients within our dataset this finding should be confirmed in a larger cohort. Many have advocated for the creation of AYA-specific programs in order to provide age-specific care and to better address the unique toxicities and psychosocial challenges that face AYAs with cancer.[32, 33] Although our data could not determine care received through AYA specialty programs, others have reported an increased use of pediatric regimens delivered to ALL patients treated at AYA centers.[34]

At a minimum, our findings support the notion that AYAs with ALL are more likely to receive pediatric ALL regimens at either pediatric centers or at adult centers that treat a higher volume of these patients. Our findings that receipt of a pediatric ALL regimen in the

adult setting are associated with NCI-cancer center designation and AYA ALL volume is, in part, related to the C10403 study, which was open to accrual from 2008 to 2012. Although this study was open at larger, academic cancer centers, it was also open to accrual at community-based cancer centers. Further, the trend towards use of adult ALL regimens at lower volume AYA ALL facilities continued through 2013-2014, supporting the notion that even after closure of this national study there continues to be a variety of approaches to the treatment of AYA ALL. Our findings suggest that use of pediatric inspired ALL regimens for AYA patients treated in the adult setting may rise with the opening of another national ALL trial aimed at AYA patients. However, AYA patients treated at low volume ALL centers often do not have access to cooperative group studies, thus widening the disparity in treatment approaches between centers caring for AYA ALL patients.

Our study intended to describe patterns of AYA ALL treatment with a population-based approach. We used choice of induction regimen as a surrogate for treatment approach. For most ALL patients the initial ALL regimen is followed throughout the treatment course; however, clinical circumstances such as refractory disease or transplantation in first remission may alter the treatment course over time. We were limited in that not every patient reported to the GBACR had usable induction treatment data, although data capture in over 70% of patients was more favorable than anticipated, and most patients without usable data were treated from 2004 to 2007, when most, if not all, AYAs with ALL were treated using adult regimens in the adult setting. Our sample size did not allow for multivariate modeling of the independent factors associated with pediatric regimens in the adult setting, which would be of interest. Importantly, results based on patients in Northern California may not represent AYA ALL patients or practice patterns across the U.S. However, use of a population-based dataset enabled us to include AYA ALL patients with a variety of racial/ethnic and socioeconomic backgrounds, including those who were uninsured, privately insured and publicly insured. Patients in our study were treated at 31 hospitals, including small community-based and larger, private hospital networks, as well as academic centers, similar to the range of AYA cancer treatment locations across the U.S.[35] Consolidation of AYA cancer care in other countries has been described.[36, 37] Finally, we did not intend this to be a study of AYA ALL outcomes, as there is already an abundance of retrospective and prospective research comparing outcomes for AYA ALL patients treated with pediatric versus adult regimens; [1-5, 7-14, 29] rather, our objective was to describe patterns of AYA ALL management over time in order to inform clinicians and researchers in the field.

In conclusion, with a population-based approach using patient facility-level data reported to the GBACR, we demonstrate general practice patterns related to the treatment of AYA ALL in the U.S. over the last decade. Our data show that as recently as 2014, AYAs with ALL were treated with a wide variety of ALL treatment protocols, the minority being pediatric-inspired ALL regimens. Additional research is needed to determine factors that contribute to AYA ALL treatment selection by adult oncologists, and to understand barriers to increasing AYA care at higher volume AYA ALL centers.

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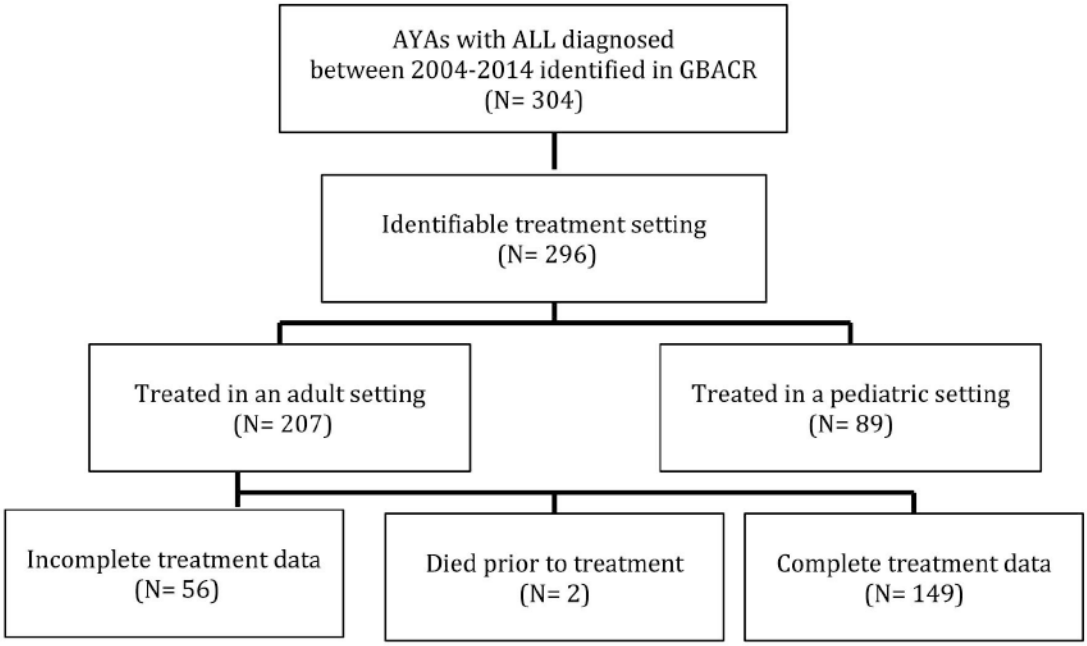

Figure 1.
Study Flow Chart

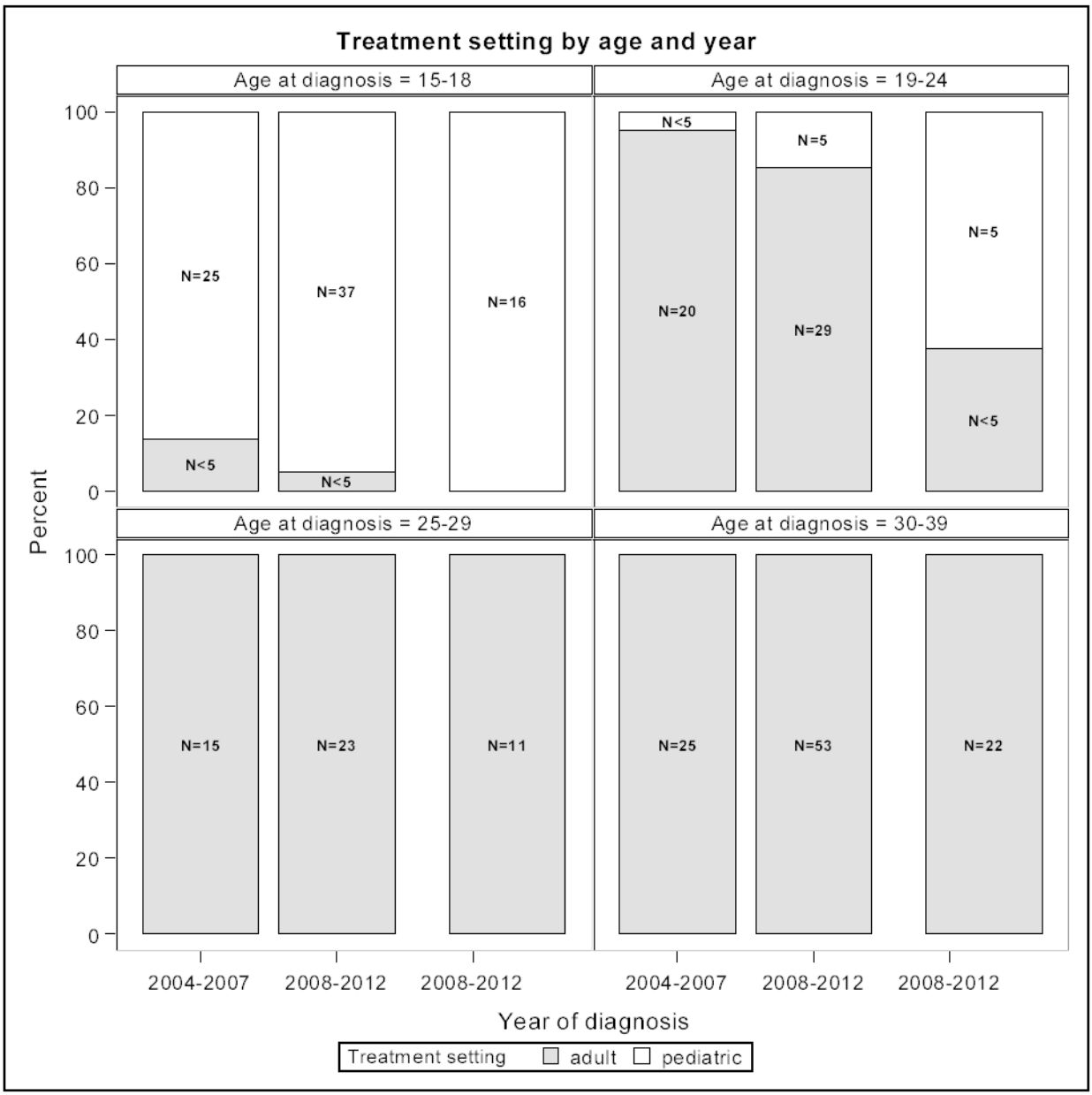

Figure 2.
AYA ALL Treatment Setting Over the Past Decade

Table 1

AYA ALL Patient and Induction Facility Characteristics by Treatment Setting, Northern California, 2004-2014

		Treatment Setting						
		Total N=296		Pediatric N=89		Adult N=207		
		N	%	N	%	N	%	*P*
Age at diagnosis, years	15-18	84	28	78	88	6	3	<.0001
	19-24	63	21	11	12	52	25	
	25-29	49	17	0	0	49	24	
	30-39	100	34	0	0	100	48	
Year of diagnosis	2004-2007	90	30	26	29	64	31	0.48
	2008-2012	149	50	42	47	107	52	
	2013-2014	57	19	21	24	36	17	
Sex	Female	121	41	29	33	92	44	0.07
	Male	175	59	60	67	115	56	
Race/Ethnicity	Asian/ Pacific Islander	61	21	27	30	34	16	0.02
	Hispanic	132	45	42	47	90	44	
	Non-Hispanic Black	11	4	<5	2	9	4	
	Non-Hispanic White	90	30	18	20	72	35	
	Other, unknown	<5	1	0	0	<5	1	
Neighborhood SES quintile	1 - Lowest	42	14	13	15	29	14	0.56
	2	44	15	18	20	26	13	
	3	59	20	16	18	43	21	
	4	61	21	17	19	44	21	
	5 - Highest	90	30	25	28	65	32	
Health Insurance Status	Insured NOS	35	12	8	9	27	13	0.65
	Medicare	<5	1	0	0	<5	2	
	Private/military	169	57	55	62	114	55	
	Public	85	29	26	29	59	29	
	Uninsured/self-pay	<5	0.3	0	0	<5	0.5	
	Unknown	<5	0.7	0	0	<5	1	

		Treatment Setting						
		Total N=296		Pediatric N=89		Adult N=207		
		N	%	N	%	N	%	*P*
Induction facility is NCI-CC	No	157	53	39	44	118	57	0.04
	Yes	139	47	50	56	89	43	
Induction facility volume*	<2 per year	81	27	7	8	74	36	<.0001
	≥ 2 per year	200	68	78	88	122	59	

SES: socio-economic status; NOS: not otherwise specified; NCI-CC: National Cancer Institute designated Cancer Center

*20 lower volume facilities, 7 higher volume facilities, 1 out of region facility without volume calculation; excludes 15 patients treated out of region or not treated

Table 2

Treatment Regimens Administered in Adult Settings to AYAs with ALL Diagnosed in the Greater Bay Area by Time Period of Diagnosis, 2004-2014

Treatment Regimen	Total N=149	2004-2007 N=36	2008-2012 N=84	2013-2014 N=29
Adult ALL Regimen	117 (79%)	36 (100%)	58 (69%)	23 (79%)
Hypercvad	45	11	23	11
Adult Cooperative Group	41	16	20	5
Linker Regimen	26	5	15	6
Other Adult Regimen	5	<5	0	<5
Pediatric Inspired Regimen	32 (21%)	0 (0%)	26 (31%)	6 (21%)
C10403 (on or off study)	27	0	24	<5
Pediatric Cooperative Group	5	0	<5	<5

Table 3

AYA ALL Patient and Induction Facility Characteristics by Treatment Regimen in Adult Setting, Northern California, 2004-2014

		ALL Regimen						
		Total N=149		Pediatric Regimen N=32		Adult Regimen N=117		
		N	%	N	%	N	%	*P*
Age at diagnosis, years	15-18	<5	3	<5	3	<5	3	0.08
	19-24	36	24	10	31	26	22	
	25-29	33	22	11	34	22	19	
	30-39	76	51	10	31	66	56	
Year of diagnosis	2004-2007	36	24	0	0	36	31	<0.0001
	2008-2012	84	56	26	81	58	49	
	2013-2014	29	19	6	19	23	20	
Sex	Female	69	46	17	53	52	44	0.43
	Male	80	54	15	47	65	56	
Race/Ethnicity	Asian/ Pacific Islander	25	17	6	19	19	16	0.28
	Hispanic	64	43	11	34	53	45	
	Non-Hispanic Black	8	5	0	0	8	7	
	Non-Hispanic White	51	34	15	47	36	31	
Neighborhood SES quintile	1 - Lowest	20	13	<5	6	18	15	0.37
	2	22	15	8	25	14	12	
	3	31	21	6	19	25	21	
	4	30	20	6	19	24	21	
	5 - Highest	46	31	10	31	36	31	
Health Insurance Status	Insured NOS	22	15	6	19	16	14	0.70
	Medicare	<5	<1	0	0	<5	<1	
	Private/military	85	57	20	63	65	56	
	Public	39	26	6	19	33	28	
	Uninsured/self-pay	<5	<1	0	0	<5	<1	
	Unknown	<5	<1	0	0	<5	<1	
Induction facility is NCI-CC	No	75	50	8	25	67	57	0.001

		ALL Regimen						
		Total N=149		Pediatric Regimen N=32		Adult Regimen N=117		
		N	%	N	%	N	%	*P*
	Yes	74	50	24	75	50	43	
Induction facility volume *	<2 per year	47	32	5	16	42	36	0.03
	≥2 per year	98	66	25	78	73	62	

SES: socio-economic status; NOS: not otherwise specified; NCI-CC: National Cancer Institute designated Cancer Center

* Excludes 15 patients treated out of region or not treated