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Clinical management of Australian AYAs with acute lymphoblastic and myeloid leukemias: a national population-based study.

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List of Abbreviations

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ANZCHOG	Australian New Zealand Children's Hematology/Oncology Group
APL	Acute promyelocytic Leukemia
ATRA	all-*trans*-retinoic acid
ATO	arsenic trioxide
AYA	adolescents and young adults
BFM	Berlin-Frankfurt-Münster
CIs	Confidence Intervals
COG	Children's Oncology Group
ECOG	Eastern Cooperative Oncology Group
EFS	Event Free Survival
HR	Hazard Ratio
ICE	Idarubicin, Cytarabine, Etoposide
OS	Overall Survival
Ph+	Philadelphia positive
Ph-	Philadelphia negative
RFS	Relapse Free Survival
UK	United Kingdom
US	United States of America

ABSTRACT

Background: While several studies have examined the treatment of adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL), studies of acute myeloid leukemia (AML) are rare. Using national data for Australia we describe i) the number and type of treatment centres caring for AYAs, ii) induction/first-line treatments and iii) survival outcomes.

Procedure: National population-based study assessing treatment of 15-24 year olds diagnosed with ALL or AML between 2007 and 2012. Treatment details were abstracted from hospital medical records. Treatment centers were classified as pediatric or adult; adult AYA-focused or other adult and by AYA volume (high/low). Cox proportional hazard regression analyses examined associations between treatment and overall, event-free and relapse-free survival outcomes.

Results: 47 hospitals delivered induction therapy to 351 patients (181 ALL; 170 AML), with 74 (21%) treated at pediatric centers. 70% of hospitals treated less than 2 AYA leukemia patients per year. Regardless of treatment centre, 82% of ALL patients were on pediatric protocols. For AML, pediatric protocols were not used in adult centres, with adult centres using a non-COG 7+3-type induction protocol (51%), or an ICE-type protocol (39%). Exploratory analyses suggested that for both ALL and AML, AYAs selected for adult protocols have worse overall, event-free and relapse-free survival.

Conclusions: Pediatric protocols were commonly used for ALL patients regardless of where treated, indicating rapid assimilation of recent evidence by Australian hematologists. For AML, pediatric protocols were only used in pediatric centres. Further investigation is warranted to determine the optimal treatment approach for AYA AML.

Introduction

Survival for many cancers in adolescents and young adults (AYAs) (those aged between 15 to 39 years in United States (US) and 15 to 25 in Australia and the United Kingdom[1]) lags behind that for children[2,3]. Although there has been some improvement in Australia[4], similar to the US[3], a difference is still seen for acute lymphoblastic leukemia (ALL) (5-year survival: 64% AYA vs. 90% children) and acute myeloid leukemia (AML) (5-year survival: 61% AYA vs. 74% children)[5]. As AYAs in Australia and the US are more likely to attend adult rather than pediatric treatment centers[6,7], treatment differences between adult and pediatric hospitals may contribute to survival differences.

In contrast to adult ALL treatment protocols, pediatric protocols involve a more intensive chemotherapy dosing regimen, response-based risk stratification, prolonged maintenance therapy, earlier and more frequent intrathecal chemotherapy, and possible differences in the anti-cancer drugs used[8-10]. While disease outcomes are influenced by a number of factors including disease and host biology, treatment toxicity and adherence, there is now also substantial evidence that ALL survival is significantly better for patients up to age 40 treated on pediatric-type rather than adult protocols[11-14]. However, a Californian study found 79% of AYAs aged 15 to 39 years with ALL treated in adult centres were still being treated with adult protocols in 2013-14, including 72% of 15-24-year-olds treated in these settings[8]. The extent to which current evidence regarding treatment of AYAs with ALL has been incorporated into clinical practice in countries outside the US is unknown.

There is less clarity regarding whether adult or pediatric protocols are more appropriate for AYA AML patients. Recent studies suggest that although survival might be better for those treated on pediatric protocols, higher post-remission treatment-related mortality in older patients on these protocols, offsets this benefit[15]. Treatment for the AML subtype Acute Promyelocytic Leukemia (APL), differs to that for AML and is generally similar for adults and children involving all-*trans*-retinoic acid (ATRA) traditionally combined with anthracycline-based chemotherapy[16]. Findings from trials published during the 2000s and 2010s, showed that the addition of arsenic trioxide (ATO) to ATRA improved outcomes and reduced toxicities for both adults and children[17-20], and 5-year survival for AYA APL is now over 80%[21]. Few studies have investigated treatment of AYA AML and APL patients at the population level.

In Australia, AYA cancer services focus on care for those aged between 15 and 24 years. Within this age group, around 1000 AYAs are diagnosed with cancer across the country annually[5] with approximately 56-60 diagnosed with ALL or AML annually. With upper age restrictions for pediatric treatment centers in Australia ranging between 15 and 17 years, most AYAs are treated at adult hospitals. In 2008, with funding from the Australian Government and philanthropic services, Canteen (the peak consumer advocacy group for AYA cancer in Australia) began working with state health departments and health services to develop specialized AYA treatment centers[22]. Co-located with the main adult or pediatric cancer services at publically-funded tertiary hospitals in each state, these services are staffed by specialist AYA medical and allied health care professionals. To ensure regional and rural patients had access to this specialist care, outreach programs or 'hub and spoke'

models of care were developed.

In this paper we use population-based data for 15- to 24-year-old Australians diagnosed with AML and ALL, to examine where AYAs with these two cancers were treated (adult or pediatric hospital, AYA volume and specialization of AYA care), what induction protocols were used and whether type of treatment centre attended influenced the protocol used. A secondary aim was to explore the relationship between survival and induction protocol for ALL and AML at the population level.

Method

Patients

People aged 15 to 24 years, diagnosed with ALL or AML (including APL) between 1/1/2007 and 31/12/2012 in the six states of Australia were eligible for this study.

Procedure

In Australia, all new cancers are reported to state-based population cancer registries which also record age, gender, residential location, cancer type, morphology and hospitals attended. Eligible patients were identified through the cancer registries in four states. In two states, cancer registries could not provide a patient list, with policy prohibiting this is one state and a major software and hardware upgrade prohibiting data requests in the second. In the first state, the cancer registry supplied a list of hospitals treating eligible cases along with the number treated, while in the second leading AYA clinicians identified treating hospitals. In both states, eligible cases were identified through hospital records.

Trained data managers attended hospitals to extract relevant data by retrospective review of medical records. If a patient attended multiple centers for cancer care, treatment details were sought from each center. Data collectors reviewed electronic and paper-based medical records at each site, including all documentation in a patient's file. Pharmacy dispensing databases and pathology databases were reviewed where possible. The study had ethical approval from each state's lead institutional ethics review body and other institutions as needed.

Data extracted

The ALL/AML/APL chemotherapy induction regimen documented in the medical record was extracted. For ALL, regimens were categorized as adult or pediatric-type. Adult ALL regimens were: hyper-CVAD, UK ALL XII/ECOG E2993, and CALGB. All Children's Oncology Group (COG) protocols were defined as pediatric regimens as were the following pediatric or pediatric-inspired protocols: BFM-based regimens; FRALLE and variants, and Hoelzer/GMALL. AML regimens were classified as non-COG variants of 7+3, variants of ICE (idarubicin, cytarabine, etoposide), COG protocols or other trials or protocols. ICE and non-COG 7+3 variants were considered adult protocols. APL regimens were classified as protocols with or without arsenic.

Date of diagnosis, baseline white cell count (in 10^{e9}/L), whether bone marrow aspiration and cytogenetics were investigated at diagnosis, date and type of stem cell transplant (SCT), induction failure, evidence of relapse and relapse date were extracted from medical

records. Although we attempted to also collect immunophenotype and cytogenetics information, this was not reliably recorded in the medical records so not reported.

Treating hospitals were classified as pediatric or adult. Adult AYA-focused hospitals were those having a defined model of care for young people, including access to clinicians (in some cases, dedicated AYA oncologists), nurses and health care professionals (social work, psychology) with AYA expertise[22]. These were generally in major cancer treatment centers. Adult hospitals without this model of care were defined as "other adult hospitals" which could include tertiary cancer treatment centres, smaller adult hospitals that treat cancer and regional treatment centres. Hospitals treating children up to age 16 or 17 were classified as pediatric.

The number of ALL and AML/APL cases treated at adult hospitals over the study period was calculated and classified into high or low AYA hematological cancer volume. Adopting the definition used in a US study examining AYA ALL cancer care[8], adult hospitals treating 2 or more AYAs ALL/AML/APL cases a year (equating to 12+ cases over the study period) were classified as high-volume AYA hospitals.

Survival data

To assess survival, data was linked probabilistically to the National Death Index using sex, date of birth and address.

Statistical analyses

Descriptive statistics characterized the sample. Diagnostic data were combined across leukemia types for chi-square analyses examining associations with treatment setting and hospital volume. Philadelphia positive (Ph+) ALL cases were excluded from analyses relating to treatment protocols and survival. Unless otherwise specified, APL cases are not included in AML data. Cases with missing data on a variable were excluded from analyses of that variable.

For survival, the last date for follow-up was 1 October 2016. Overall survival (OS) was defined as time from diagnosis to death. Event-free survival (EFS) was defined as time from diagnosis to death, relapse or induction failure. Relapse-free survival (RFS) was defined as the time from diagnosis to relapse or death for those who did not fail induction. Patients who did not have the outcome of interest (e.g., death) by 1 October 2016 were censored. Cox proportional hazards examined the influence of protocol type after adjusting for age and hospital volume on OS, EFS and RFS. Sex and baseline white cell counts were controlled in these analyses. Given small numbers for some comparison groups, these analyses are exploratory in nature. Analyses were conducted using STATA v.14 using a significance level of $p<.05$ (two-tailed).

Results

Sample Characteristics

Data were collected on 351 patients; 181 ALL (73% B-cell, 24% T-cell; including 6 Ph+), and 170 AML (including 39 APL). In states where CaRs identified patients, data were collected on 92% of eligible cases. 58% of AYAs with ALL were older than 18 years when diagnosed, as

were 67% of those with AML (Table 1).

Forty-four hospitals were involved in patients' diagnosis and 47 hospitals delivered induction therapy (Figure 1), most commonly an adult AYA-focused hospital (Table 1). Thirty-three of the 47 hospitals (70%) were low-volume AYA hospitals. Most 15- (84%) and 16-year-olds (65%) attended a pediatric hospital for treatment (Table 2), while most 18-24-year-olds were treated in adult hospitals (148 attended an adult AYA-focused hospital and 72 attended other adult hospitals).

Median number of days from diagnosis to treatment start was 2 (range: 0-29) for ALL and 2 (range: 0-47) for AML (including APL).

Chemotherapy Protocol*:*

Adult versus Pediatric Hospitals: For ALL patients, type of treatment center was related to protocol. Pediatric protocols were used for all patients attending pediatric hospitals, and for 77% of patients attending adult hospitals (p<.01; Table 2). Year of diagnosis was not linearly related to the use of pediatric protocol for ALL (2007: 87%, 2012: 73%; p=0.783)

For AML there was a significant difference between pediatric and adult hospitals in induction protocols used (p<.01; Table 2). AML pediatric protocols (generally COG or ANZCHOG AML protocol) were used for 86% of patients attending pediatric centers but were not used in any adult hospitals. AML patients attending adult centers were treated with 7+3-type (51%) or ICE-type (39%) protocols. Proportions of AML cases treated on

pediatric or adult protocols did not change over the study period. However for AYAs on adult protocols, the proportion on 7+3-type protocols increased from 29% in 2007 to 94% in 2012 (p=0.03).

Seven of the 33 APL cases treated in adult hospitals received a protocol that did not include arsenic (Table 2). There was no evidence of a relationship between hospital type and protocol type. The number of APL patients on protocols containing arsenic changed little over the study period (2008: 5 of 6 patients; 2011: 7 of 8; 2012: 4 of 8).

Adult Hospitals' AYA Volume and AYA-Focus: There were few differences in the management of cases attending adult AYA-focused or other adult hospitals or between high- or low-volume adult hospitals (Table 2). In patients attending adult hospitals, protocols for ALL, AML, and APL did not differ by hospital characteristics.

Induction failed for 12 ALL (7%) and 13 AML (10%) patients. Protocol type was not related to induction failure for ALL or AML. Thirty-three percent of ALL patients, 49% of AML patients and 1 APL patient had a SCT. Of the 25 patients whose induction failed, 17 had a SCT (ALL: n=6; AML: n=11). ALL Philadelphia negative (Ph-) patients on adult protocols were more likely to have a SCT (60%) than those on pediatric protocols (26%) (p<.001). Most patients (90%) having SCT had an allogenic SCT.

Relapse and Survival

At data collection, ALL patients had been followed-up for a median of 45 months (range: 1-

98), AML for a median of 49 months (range: 2-95) and APL for 44 months (range: 13-85). Median time from diagnosis to date of follow-up for survival analyses for both ALL and AML was 66 months (range:0-116) and 72 months (range:40-108) for APL. Twenty-six per cent of ALL, 42% of AML and 8% of APL patients had relapsed by date of data collection. The median time between diagnosis and relapse was 15 months for ALL (range:1-62), 10 months for AML (range:2-39). Only 3 people with APL relapsed with one at 7 months, 1 at 28 months and 1 at 31 months post diagnosis. 5-year OS was 73% for ALL, 69% for AML and 97% for APL. Of ALL patients, 33 of 46 patients with relapsed disease (72%) and 18 of the 134 without relapsed disease (13%), had died by end of follow-up. For AML, 34 of 54 (63%) relapsed patients and 9 of the 77 (12%) patients without relapsed disease had died. Of patients who died without relapsing, nine ALL patients and one AML patient died within six months of diagnosis.

Kaplan-Meier functions for OS, EFS and RFS for ALL Ph- cases by protocol type are shown in Figure 2. Adult protocols were associated with lower OS, EFS and RFS compared to pediatric protocols, although log rank tests were not significant. In Cox regression analyses, after adjusting for age at diagnosis and treatment centre AYA-volume, pediatric protocols were associated with better OS, EFS and RFS (Table 3). Kaplan-Meier functions for OS, EFS and RFS for AML cases by protocol type are shown in the lower half of Figure 2. The better outcomes for those on pediatric protocols were also evidenced in the Cox regression analyses with pediatric protocols consistently associated with better OS, EFS and RFS (Table 3), although these associations were not statistically significant.

One APL case died during the study period with this case relapsing before data collection. The case who died was on a protocol containing arsenic while those who relapsed were on non-arsenic containing protocols.

Discussion

This national study provides, for the first time, information on the clinical treatment of acute leukemias in Australian AYAs, with an exploratory examination of survival also presented. A large number of hospitals were involved in the treatment of AYAs with these cancers, and around 70% of these hospitals treated less than two cases per year. However, regardless of where ALL Ph- patients were treated, most were on pediatric protocols. For AML, only patients treated at a pediatric centre were on a pediatric protocol, with patients treated at adult treatment centres on adult protocols most commonly adaptations of the non-COG 7+3 protocol. Type of adult treatment centre did not seem to influence the protocol used for AYA AML. Most APL cases were on a protocol that contained arsenic.

Most AYA ALL patients treated in adult treatment centres were treated on a pediatric protocol. This contrasts US data showing that only around 28% of 15-24-year-olds with ALL treated in adult settings were on pediatric protocols[8]. Unfortunately, as previous studies have examined treatment location rather than protocol[23,24], have not assessed actual treatment patterns[25], or have examined appropriateness of total care, there are few studies with which we can compare our data. Our data suggest that, at least by the late 2000s, most hematologists working in adult centers in Australia had incorporated the growing body of

evidence for treating AYA ALL patients on pediatric protocols into their clinical practice.

The literature is not clear regarding the preferred treatment protocol for AYA AML patients[26]. In this Australian study, variants of non-COG 7+3 and ICE-type protocols were most common for AML patients in adult hospitals, with non-COG 7+3-type protocols becoming more common over the study period, possibly reflecting changes in the Australian Leukaemia and Lymphoma Group's choice of induction regimen for their clinical trials during this time. While 86% of AML patients treated in pediatric hospitals were on COG protocols pediatric protocols were not used in adult hospitals. This finding suggests that adult clinicians do not consider these more intensive protocols suitable for AML patients over the age of 18 or may be unaware of pediatric AML approaches. For APL, although the number of cases in our study was small, regardless of where these patients were treated, most were on protocols containing arsenic.

In adult hospitals, the volume of AYA ALL/AML patients did not influence the type of protocol used for either disease. While this contrasts with a US study's finding that ALL patients attending adult hospitals were more likely to be on a pediatric protocol if the hospital treated ≥2 ALL AYA patients a year[8], it is in line with other studies that have not found associations between hospital patient volume and medical care for AYA cancer patients[27]. Following the US study[8] we classified hospitals treating an average of 2+ patients a year as high volume. Due to Australia's small population, this cut-off value resulted in treatment centers with expertise in care of other cancers being classified as low volume and this may have influenced our findings.

The greater use of pediatric regimens in adult hospitals regardless of volume in Australia may be due to the influence of national groups such as Canteen, the Clinical Oncology Society of Australia (COSA), Australian and New Zealand Haematological Oncologists Group (ANZCHOG), the Australasian Leukaemia and Lymphoma Group (ALLG) and trial groups, which have ensured education programs for clinicians, nurses and allied health regarding best practice care for AYAs including use of pediatric protocols. The development of AYA services that cross pediatric and adult hospitals during our study period is also likely to have increased collaboration, support and expertise in using pediatric protocols and managing any resulting side-effects. A move towards network-wide clinical multidisciplinary team meetings to plan and oversee therapy during our study period may have also helped to ensure all treatment centres have access to clinical expertise. Finally as many clinicians work across a number of different treatment centres, this may help to increase clinical expertise at low volume hospitals.

The Australian ALL 5-year survival estimates are similar to those reported from France[23] and the UK[28] and better than those reported for similarly aged patients from the US[24,29,30]. We found almost a halving of the HR associated with OS, and reductions between 33% and 40% for EFS and RFS for ALL patients treated on pediatric-type protocols compared to those on an adult protocol. While our differences were not statistically significant, our pattern of results is consistent with findings from trials comparing outcomes from young people participating in pediatric and adult clinical trials[12,14,31] and other studies[32].

Comparisons of 5-year survival rate for AML patients in our study with other work is problematic due to differences in diagnosis periods. A study of Californian 15- to 21-year-olds diagnosed between 1996 and 2008 found a 5-year survival rate of 49%[24],. Another study comparing AML survival between Germany and the US, reported 5-year survival for 15- to 24-year-olds diagnosed between 1997 and 2011 was 55% in the US and 65% in Germany[29]. . Our consistent pattern for better OS, EFS and RFS for those on COG protocols compared to adult protocols are in line with results from studies comparing outcomes for AML patients treated in pediatric compared to adult clinical trials[15] and those comparing outcomes for patients under 18 years and those aged 18-30 years[30]. Increasing age is an important negative prognostic factor for AML[33]. While recent pediatric protocols can produce similar survival outcomes for patients aged 10 to 21 as for children under 10, treatment-related toxicity is greater for older patients[34]. While age was controlled for in our analyses, it is likely that some confounding remained and this may have contributed to our results.

Strengths of this study include its population-based approach to case inclusion, the high ascertainment rate for data collection and its national focus. These strengths ensure that the study can comprehensively describe care patterns for acute leukemia AYA patients in Australia. However, several limitations need to be acknowledged. As the study involved medical record review, data are only as accurate as the information recorded. Gaps in the medical record, could lead to under-reporting of treatment delivered and misclassification of care. Second, while we attempted to document all chemotherapy information for each patient, it was often difficult to record dose and intensity. Hence, we cannot report the extent to

which the protocol was delivered as planned. While we took care to appropriately classify pediatric and adult protocols, classification of regimens is not clear cut due to the evolution of protocols which may be based on both adult and pediatric experience. For instance two ALL cases on a CALGB protocol were classified as on an adult protocol as we could not determine whether this referred to the more recent pediatric inspired CALGB protocol (C10403) or an earlier adult-type protocol. However, any misclassification would have minimal effect on results. We could not accurately classify patients by their genetic and/or molecular risk status and therefore our survival analyses have not adjusted for this important prognostic indicator. Further second line or subsequent treatment protocols are considered in survival analyses. Despite a national population study covering multiple years with almost complete ascertainment of cases, the sample size of ALL and AML cases was still relatively small. While this highlights the relative rarity of these cancers, the small sample size limits our ability to demonstrate any significant differences in treatment by hospital setting or volume and in survival by treatment protocol. Despite these limitations, this population-based study describes for the first time the treatment patterns for Australian AYA ALL and AML patients. Our study suggests that regardless of where they are treated most AYA ALL patients are receiving best practice care, although the 18% of ALL patients treated on adult protocols suggest improvements can be made. Although pediatric AML protocols were only used in pediatric treatment centres, AML patients treated in adult treatment centers are increasingly likely to be treated on a 7+3-type protocol, which is very similar to the chemotherapy backbone of most paediatric regimens. Our study suggests the survival benefits of treating ALL AYA patients on pediatric protocols found in clinical trials are evidenced at the general population level in Australia.

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Figure legends

Figure 1. Number of AYA ALL and AML/APL patients treated with chemotherapy at each hospital in the study period, by type of treatment center.

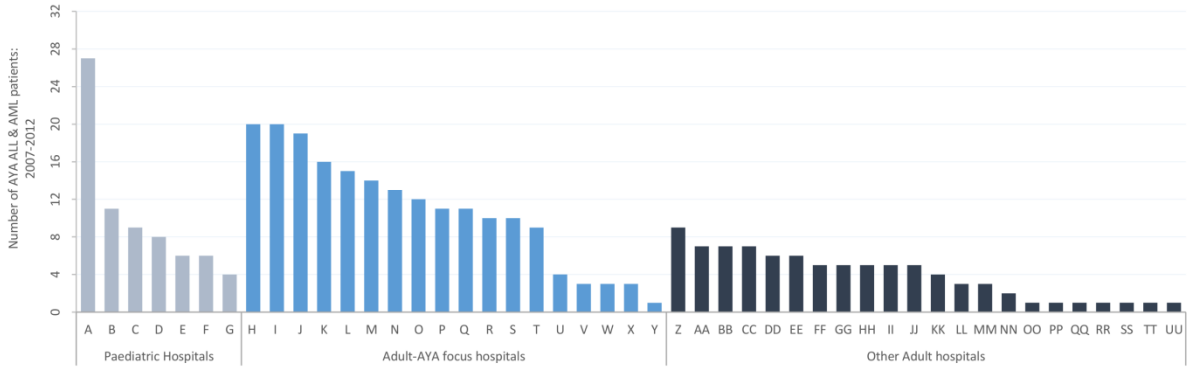

Figure 2: Overall survival, event free survival and relapse free survival Kaplan Meier functions for ALL (above) and AML (below) for cases on a pediatric or adult induction protocol. 5-year survival estimates (and 95% Confidence intervals) shown as text. P-value for Log rank test for equality of survivor functions shown. Time since diagnosis capped to 6 years in graphs. Relapse free survival excludes cases where induction failed, but all cases are included in other analyses.

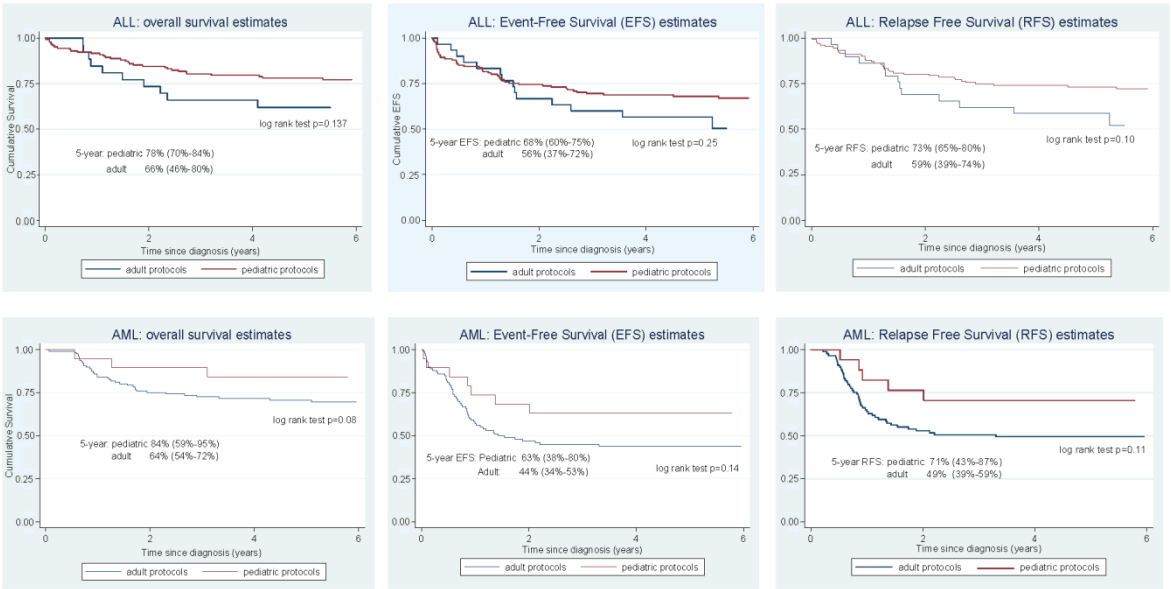

Table 1: Demographic, and treatment setting characteristics for each tumor type.

	ALL N=181	AML N=131	APL N=39
Age at diagnosis (years)			
15	24 (13%)	9 (7%)	4 (10%)
16	27 (15%)	15 (12%)	1 (3%)
17	26 (14%)	19 (15%)	5 (13%)
18-24	104 (58%)	88 (67%)	29 (74%)
Gender[a]			
Male	133 (74%)	71 (54%)	19 (49%)
Female	48 (27%)	59 (45%)	20 (51%)
Location of residence[b]			
Greater metropolitan area (capital city)	123 (68%)	101 (77%)	25 (64%)
Regional area	57 (32%)	30 (23%)	14 (36%)
Treatment conducted at			
Adult-AYA-focused hospital	99 (55%)	73 (56%)	22 (56%)
Other Adult hospital	39 (22%)	36 (28%)	11 (28%)
Pediatric hospital	43 (24%)	22(17%)	6 (15%)

Note: Percentages may not add to 100 due to rounding.
ALL: acute lymphoblastic leukemia; AML acute myeloid leukemia; APL: acute promyelocytic leukemia
[a] One additional AML patient identified as transgender.
[b] N=180 ALL cases due to missing postcode data

Table 2: Treatment protocols for ALL, AML and APL cases by characteristics of hospital attended

	Total	Type of hospital		Adult hospitals only			
		Adult	Pediatric	Focus		Volume	
				AYA	Other Adult	Low	High
	N=351	N=280	N=71	N=195	N=85	N=161	N=116
All cases							
Age at diagnosis (years)[a]							
15	37 (11%)	6 (16%)**	31 (84%)	6 (100%)	0	2 (33%)	4 (67%)
16	43 (12%)	15 (35%)	28 (65%)	14 (93%)	1 (7%)	10 (68%)	5 (33%)
17	50 (14%)	39 (78%)	11 (22%)	26 (67%)	13 (33%)	20 (51%)	19 (49%)
18-24	221 (63%)	220 (100%)	1 (0.5%)	149 (68%)	71 (32%	129 (59%)	88 (41%)
Induction protocols							
ALL[b]	*(N=171)*	*(N=129)*	*(N=42)*	*N=91*	*N=38*	*N=76*	*N=52*
Pediatric	141 (82%)	99 (77%)**	42 (100%)	72 (79%)	27 (71%)	56 (74%)	42 (81%)
Adult	30 (18%)	30 (23%)	0	19 (21%)	11 (29%)	20 (26%)	10 (19%)
AML	*N=131*	*N=109*	*N=22*	*N=73*	*N=36*	*N=63*	*N=44*
COG protocols	19 (15%)	0**	19 (86%)	n/a	n/a	n/a	n/a
7+3-type protocols	55 (42%)	55 (51%)	0	37 (51%)	18 (50%)	30(48%)	24 (55%)
ICE-type protocols	45 (34%)	43 (39%)	2 (9%)	30 (41%)	13 (36%)	27 (43%)	16 (36%)
Other (including unclear/missing)	12 (9%)	11 (10%)	1 (5%)	6 (8%)	5 (14%)	6 (10%)	4 (9%)
APL	*N=39*	*N=33*	*N=6*	*N=22*	*N=11*	*N=17*	*N=16*
Protocols including arsenic	31 (79%)	26 (79%)	5 (83%)	16 (83%)	10 (91%)	15(88%)	11 (69%)
Protocols not including arsenic	8 (21%)	7 (21%)	1 (17%)	6 (27%)	1 (9%)	2 (12%)	5 (31%)

Note: Sample sizes vary due to missing data. Percentages may not add to 100 due to rounding.
ALL: acute lymphoblastic leukemia; AML acute myeloid leukemia; APL: acute promyelocytic leukemia
[a] Percentages should be interpreted as "percentage of age group who attended an adult hospital or pediatric hospital".
[b] Excludes 6 cases that were Philadelphia positive.
** association with hospital characteristic significant at p<.01

Table 3: For ALL and AML cases, Hazard Ratios (HR) and 95% confidence Intervals (CI) from Cox regression analyses for overall survival, event free survival and relapse free survival (adjusted for sex and baseline white cell count).

	ALL[a]			AML		
	HR	95% CI	*p-value*	HR	95% CI	*p-value*
Overall survival						
Protocol type						
Adult	1			1		
Pediatric	0.51	0.24-1.06	*0.070*	0.55	(0.15-2.05)	*0.373*
Hospital case volume						
Low (< 2 cases/year)	1			1		
High (2+ cases/year)	0.99	0.54-1.82	*0.978*	0.92	(0.8-1.78)	*0.806*
Age at diagnosis (years)	0.94	0.84-1.06	*0.311*	1.07	(0.95-1.22)	*0.262*
Event Free survival						
Protocol type						
Adult	1			1		
Pediatric	0.66	0.34-1.26	*0.204*	0.42	0.16-1.08	*0.072*
Hospital case volume						
Low (< 2 cases/year)	1			1		
High (2+ cases/year)	0.77	0.46-1.31	*0.374*	0.87	0.51-1.47	*0.600*
Age at diagnosis (years)	0.97	0.88-1.07	*0.526*	0.98	0.89-1.09	*0.717*
Relapse Free survival[b]						
Protocol type						
Adult	1			1		
Pediatric	0.58	0.29-1.15	*0.120*	0.39	0.13-1.08	*0.071*
Hospital case volume						
Low (< 2 cases/year)	1			1		
High (2+ cases/year)	0.70	0.39-1.27	*0.244*	0.94	0.53-1.71	*0.860*
Age at diagnosis (years)	0.98	0.89-1.09	*0.745*	0.95	0.85-1.06	*0.297*

ALL: acute lymphoblastic leukemia; AML acute myeloid leukemia;
Sex and baseline white cell count controlled in analyses.
[a] Excludes 6 cases that were Philadelphia positive.
[b] Excludes cases where induction failed.