Title: Stage at diagnosis for children with blood cancers in Australia: application of the Toronto Paediatric Cancer Stage Guidelines in a population-based national childhood cancer registry

Running title: Stage at diagnosis for childhood blood cancers

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Abbreviations: ACCR – Australian Childhood Cancer Registry; ALL – acute lymphoblastic leukemia; AML = acute myeloid leukemia; CNS – central nervous system; COG – Children's Oncology Group; HL – Hodgkin lymphoma; ICC-3 – International Classification of Childhood Cancers, 3rd edition; NHL – non-Hodgkin lymphoma; TNM – tumor-node-metastasis; UICC – Union for International Cancer Control.

Abstract

Background: Information on stage at diagnosis for childhood blood cancers is essential for surveillance but is not available on a population basis in most countries. Our aim was to apply the internationally-endorsed Toronto Paediatric Cancer Stage Guidelines to children (<15 years) with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL) and to assess differences in survival by stage at diagnosis.

Procedure: Stage was defined by extent of involvement of the central nervous system (CNS) for ALL and AML and using the Ann Arbor and St Jude-Murphy systems for HL and NHL, respectively. The study cohort was drawn from the population-based Australian Childhood Cancer Registry, consisting of children diagnosed with one of these four blood cancers between 2006-2014 with follow-up to 2015. Five-year observed survival was estimated from the Kaplan-Meier method.

Results: Stage was assigned to 2,201 of 2,351 eligible patients (94%), ranging from 85% for AML to 95% for ALL, HL and NHL. Survival following ALL varied from 94% (95% CI=93%-95%) for CNS1 disease to 89% (95% CI=79%-94%) for CNS2 ($p=0.07$), while for AML there was essentially no difference in survival between CNS- (77%) and CNS+ disease (78%; $p=0.95$). Nearly all children with HL survived for five years. There was a trend ($p=0.04$) towards worsening survival with higher stage for NHL.

Conclusions: These results provide the first population-wide picture of the distribution and outcomes for childhood blood cancers in Australia by extent of disease at diagnosis and provide a baseline for future comparisons.

Introduction

Together, leukemia and lymphoma comprise almost half (44%) of all cancers diagnosed worldwide among children aged under 15 years.¹ Survival for children with these malignancies (collectively referred to here as “blood cancers”) has improved dramatically over the last few decades.^{2,3} These gains have largely come about as a result of international collaborative clinical trials that have led to the introduction of risk-stratified therapy and a small number of effective, targeted therapies.^{4,5}

Data on stage at diagnosis are essential to interpret and compare survival over time and between populations; however, stage data are generally lacking in population cancer registries,⁶ particularly for childhood cancers. To address this gap, an international expert panel including paediatric oncologists, epidemiologists, cancer registrars and advocacy stakeholders met in 2014 to review the major staging systems in current clinical use for 16 types of childhood cancer. A consensus was reached on the most appropriate system for use for each of these cancers in population registries.⁶ The recommendations were published as the Toronto Paediatric Cancer Staging Guidelines⁶ (referred to hereafter as “the Toronto Guidelines”) and have subsequently been endorsed by the Union for International Cancer Control (UICC) TNM Prognostic Factors project.⁷

The feasibility of using the Toronto Guidelines in practice has been evaluated in Australia within the context of the national childhood cancer registry.⁸ Using data items extracted from medical records and applying staging algorithms derived directly from the Toronto Guidelines, we found that cancer stage could be efficiently and cost-effectively assigned for the large majority of a random sample of patients with blood cancers. Routine on-site data collection at the major pediatric treating hospitals throughout Australia has consequently been expanded to include the additional data items required to assign stage. The purpose of the current paper is to report the distribution of incident cases and survival of childhood blood cancers by stage at diagnosis at the population level in Australia.

Methods

Cases were ascertained from the Australian Childhood Cancer Registry (ACCR), a national database containing details on all cases of cancer occurring in children who were aged under 15 years at diagnosis. Notification of cancer is mandatory in Australia. Information on incident cases is provided to the ACCR by the cancer registry in every State and Territory, supplemented with additional detailed data collected from the treating hospitals. These dual processes require approval from multiple ethics committees. Records in the ACCR are also regularly matched with the National Death Index to ensure accurate and complete follow-up of mortality of registered patients.

For the purposes of the current study, we focused on the four blood cancers included in the Toronto Guidelines: lymphoblastic leukemia (ALL); acute myeloid leukemia (AML); Hodgkin lymphoma (HL); and non-Hodgkin lymphoma (NHL), each defined according to the International Classification of Childhood Cancers, version 3 (ICCC-3).⁹ The study cohort comprised children resident in Australia who were diagnosed with one of these blood cancers between 2006 and 2014. Almost all Australian children with cancer are treated at a public/government-funded tertiary paediatric hospital, of which there were ten located throughout the country during the period of this study. Children whose medical records could not be located at one of these hospitals (for example, those diagnosed on the basis of death certificate or autopsy only) were excluded from the study.

Summary definitions for the stage categories by cancer type are provided in Table 1 and full details are available elsewhere.^{6,10} On the basis that the level of involvement of the central nervous system (CNS) has been shown to have prognostic importance for acute lymphoblastic leukemia,^{11,12} the Toronto Guidelines recommend the classification used by the Children's Oncology Group (COG)⁶ as the best available measure of the extent of disease at diagnosis. The association between CNS involvement and survival for children with acute myeloid leukemia is less clear.¹³ Hence a simplified version of the COG staging

system was endorsed.⁶ The Toronto Guidelines also sanction the well-established Ann Arbor¹⁴ and St Jude-Murphy¹⁵ staging systems for children with Hodgkin lymphoma and non-Hodgkin lymphoma respectively.

Data items required to assign stage were manually collected from patients' medical records by two clinical coders from the ACCR, following the same protocol as in the original study.⁸ For the purposes of quality assurance, data collection for a random sample of approximately 20 cases per type of cancer was conducted independently by both clinical coders. The full medical record was examined, including admission notes, doctors' letters, test results from diagnostic imaging, cytology, histology and hematology and physical examination reports (as relevant). A custom-built software application was used to record the relevant data for each type of cancer and stage was then automatically assigned.

The Toronto Guidelines recognise that a one size fits all approach towards staging childhood cancers is not practical globally due to variation in the resources available to population registries in different countries.⁶ A tiered approach was therefore endorsed, allowing for a less detailed staging system for use in lower resource settings (Tier 1) and a more detailed system in higher resource settings (Tier 2). For AML and HL, the two tiers are identical; for ALL and NHL, the categories are structured so that Tier 2 can be directly collapsed to Tier 1 to retain comparability. Stage was defined according to the more detailed Tier 2 categories for the current study (see Table 1).

Estimates of five-year observed survival by cancer stage for the study cohort were calculated using the Kaplan-Meier method. Mortality data were available to 31 Dec 2015, allowing a minimum of one year of potential follow-up per patient. Survival time commenced from the date of diagnosis and accumulated until either the date of death, the end of the follow-up period, or five years after diagnosis, whichever occurred first. The survival time of children who were still alive either five years after diagnosis or on 31 Dec

2015 was censored at the relevant date. Differences in survival were assessed using the log-rank test at the 95% level of significance. Stata/SE version 15.1 for Windows (StataCorp LLC, College Station, TX) was used to perform the data analysis.

Results

Medical records were located in one or more of the ten hospitals included in the study for 2,350 (94%) of the 2,501 children diagnosed with ALL, AML, HL or NHL in Australia between 2006-2014. Patients with sufficient information to enable Tier 2 stage to be assigned (n=2,202, 94% of those with medical records and 88% of all patients) formed the study cohort. Only three children (0.1%) were diagnosed based solely on either autopsy or death certificate. The proportion successfully staged varied from 85% for AML (241 of 282 cases) to around 95% for each of the remaining three blood cancers - 1,469 of 1,550 cases for ALL, 191 of 202 cases for HL and 301 of 316 cases for NHL.

Table 2 summarises the distribution of the study cohort by age, sex and mortality status (as at 31 Dec 2015). The majority were boys (58%), particularly for NHL (75%). Median age at diagnosis ranged from 4 years for children with ALL or AML to 12 years for HL.

A total of 174 children (8%) in the study died from any cause by the end of 2015 (Table 2). Most deaths (n=156, 90%) were due to the original cancer, while the remaining deaths were either as a result of a different type of cancer (n=7, 4%) or a non-cancer cause/not specified (n=11, 6%). The highest proportion of deaths was for children with AML (n=56 of 241 patients, 23%). Only two deaths (1% of cases) were recorded among HL patients.

Distribution of incident cases by stage

By far the most common category among children with ALL was CNS1 (91%), with only 2% of ALL cases classified as having CNS3 disease at diagnosis (Figure 1). Among AML patients, CNS- was around twice as common as CNS+ (66% and 34%, respectively).

For children with HL, 28% had systemic symptoms (denoted as B in the Ann Arbor staging system) recorded. Although the presence or absence of these symptoms contributes to the staging system for HL, they were combined for the purposes of this study to enable sufficient numbers for analysis. There was no clear pattern for stage among children with HL, with 29% being stage IVA/IVB at the time of presentation, the highest stage within the Ann Arbor system. In particular, 44% of those with B symptoms were diagnosed at stage IVB. More than half (56%) of the children with NHL were diagnosed at stage III, with a further 22% presenting with stage IV disease.

Observed survival by stage

The overall difference in survival by stage for ALL was of borderline statistical significance ($p=0.07$; Table 3 and Figure 2). There was however, a significant difference when comparing survival for ALL patients with CNS1 against CNS2 only (94% versus 89%, $p=0.05$) but not for CNS2 against CNS3 only (89% versus 90%, $p=0.91$). Survival estimates were similar for AML patients irrespective of CNS involvement (77% for CNS- versus 78% for CNS+, $p=0.94$).

Almost all children with HL survived for at least 5 years, without any difference apparent ($p=0.30$) by stage. Although the overall effect of disparities in survival by stage was not statistically significant for children with NHL ($p=0.22$), there was evidence of a decreasing trend in survival as stage become higher, with survival of 97% for stage I compared to 85% for stage IV ($p_{\text{trend}}=0.04$).

Quality assurance

The same stage was assigned independently by each of the two clinical coders for 76 of the 79 cases (96%) included in the random sample, including 20 of 20 (100%) for ALL, 21 of 21 (100%) for AML, 16 of 19 (84%) for HL and 19 of 19 (100%) for NHL. The few

differences were due to either varying interpretations of the raw data contained in the medical records or the discovery of additional information by one of the clinical coders; all discrepancies were resolved by consensus after further review.

Discussion

Whilst there is some variability in treatment protocols used across Australian pediatric oncology centres for blood cancers, all are active members of major international collaborative groups such as the Children's Oncology Group (COG) and International Berlin-Frankfurt-Münster (I-BFM), with blood cancer patients being either enrolled on open phase II-III clinical trials or treated according to the standard arm of contemporary protocols. Outcomes for childhood cancer, including blood cancers, in Australia are similar to those in other Western countries.¹⁶ Our results thus typify the much improved survival rates that are now achieved across most childhood blood cancers in high income countries, in what has been described as "one of the great medical success stories of the 20th century".² In particular, we have been able to establish at the population level that 5-year survival was around 80% even in ALL and NHL patients presenting with higher stage disease.

Leukemia

We are unaware of any other published, population-based studies of the stage-specific distribution or survival following childhood leukemia. Some results are available from various clinical trial groups, although comparisons are somewhat hindered by the population-based nature of our cohort versus the selected cohort of clinical trial participants.

The proportion of CNS1 disease among ALL patients in our study was 91%. A recent analysis of 9,350 patients treated on 3 Children's Oncology Group trials (AALL0331, AALL0232, and AALL0434) found that 8,030 (86%) had CNS1 disease.¹⁷ Thus, the

Australian population-based proportion of CNS1 disease, while somewhat higher, is not substantially more so than the COG experience. We do, however, acknowledge that the proportion of CNS1 in these particular COG trials is higher than that reported by other cooperative groups.^{18,19}

Assigned stage was identical (100% agreement) for both clinical coders in the double-staging sample for ALL, suggesting that data quality is unlikely to be the main cause for differences in the incident distribution of stage among children with ALL in Australia compared to elsewhere. Another possible explanation is that traumatic lumbar punctures (leading to CNS2 or CNS3 status) have been associated with less experienced practitioners.²⁰ As paediatric oncology care in Australia is delivered almost exclusively through specialist centres, it is possible that the incidence of traumatic lumbar punctures is lower than in other jurisdictions where patients are seen in a wider variety of settings. This is a hypothesis only, and further studies may be warranted to examine whether the proportion of traumatic lumbar punctures varies between populations.

A Nordic study that was restricted to “high risk” ALL patients found no statistically significant difference in survival for CNS1/CNS2 patients combined compared to CNS3.²¹ As may be expected, their estimate of 5-year overall survival for CNS3 ALL patients was also considerably lower compared to our result (71% versus 90%, respectively).²¹ Others have reported an absence of variation in event-free survival by CNS stage for childhood ALL.²² Recent studies have suggested that the outcome for children with CNS2 ALL may be similar to those with CNS3 ALL, depending on the treatment protocol used.¹² We only found a significant difference in survival for CNS1 versus CNS2, although our comparisons were limited by the smaller number of children with CNS2 or CNS3 disease in the study cohort. CNS involvement among children with ALL has been associated with other adverse prognostic features such as higher leukocyte counts and unfavourable cytogenetics.¹⁹

In line with what we have reported here, CNS involvement has been shown in clinical trials elsewhere to have a negligible impact on overall survival for children with AML,²³⁻²⁵ even though relapse is more common in the presence of CNS disease. This is at least in part because intrathecal chemotherapy has proven to be effective in the treatment of CNS disease associated with AML, but the optimal regime is yet to be determined.^{23,24} Prognosis for AML is instead primary dictated by cytogenetic and molecular characteristics at diagnosis,²⁶ raising the question of whether an alternative definition of stage for children with AML that incorporates these characteristics may be of more benefit. The availability and collection of such data by population registries could, however, prove to be an insurmountable barrier to implementation.

Notwithstanding our null result, it should be noted that population-based survival for Australian children with AML reported here (77% for CNS- and 78% for CNS+) was considerably higher than clinical trial results across four European study groups (67% for CNS- and 64% for CNS+) or in North America (61% for CNS+),^{23,24} but similar to a recent French study (71% for CNS- and 76% for CNS+)²⁵. This disparity seems counter-intuitive given that the sickest children are generally less likely to go on clinical trials; possible reasons for differences in survival across jurisdictions are thus unknown and may merit further investigation.

Lymphoma

The staging systems endorsed in the Toronto Guidelines for both HL¹⁴ and NHL¹⁵ have been in common usage for a few decades. Consequently, results from some other population-based studies were available for comparison. The Swedish Childhood Cancer Registry reported that 11% of children with HL presented with stage IV disease,²⁷ whereas data produced from the SEER*Stat package²⁸ from the United States showed 21% of cases between 2006-2014 were reported as being stage IV using the Ann Arbor staging system, in comparison to our result of 29%. Possible reasons for this difference are that the

Swedish study included children aged 0-17 (median age of 14 compared to 12 in our study) and went back further in time (1985-2009). Of interest, the proportion identified with stage III or IV in Sweden almost doubled in later years, most probably due to improvements in imaging techniques.²⁷ An alternative explanation may be that Australian children with HL experience prolonged times to diagnosis leading to higher stage disease; this theory remains to be tested. Smith et. al.²⁹ reported that among adolescents and young adults with HL in California, those without health insurance had an increased chance of being diagnosed with higher stage disease. This is unlikely to be the reason for our results, given that public health care is provided free of charge in Australia. Data quality for HL in our study was lower (84% agreement between the clinical coders) than for the other blood cancers, which may also have contributed to this finding.

The prognosis for children diagnosed with HL is generally very good,^{30,31} as reflected in our cohort. In particular, all 55 Australian children (100%) with stage IV disease remained alive for up to five years from their date of diagnosis. Higher stage has, however, been identified as a prognostic factor associated with decreased event-free survival following multivariable analysis in some institutional or clinical studies involving children with HL.^{32,33}

The percentage of children with NHL presenting with stage IV disease in Australia (22%) was similar to results from Sweden (21%)³⁴ but slightly higher than for the five Nordic countries (16%).³⁵ Despite both of these population-based studies using the same staging system as we did,¹⁵ it should be noted that they were published around 20 years ago which could affect comparability in regard to issues such as data quality. Our lack of a significant difference in survival by stage at diagnosis for NHL may be at least in part due to the relatively small number of children in the analysis, with 5-year observed survival ranging from 97% for stage I to 85% for stage IV. In comparison, survival rates for childhood NHL in the United States are reported to vary from over 95% to approximately 70%, depending on stage and histology.³⁶

Strengths and limitations

Use of the Australian Childhood Cancer Registry meant that our cohort was representative of the entire population of Australian children with blood cancers. However, the relatively small numbers of cases, particularly when stratified by stage, precluded the use of multivariable models. This meant that our survival estimates by stage are not adjusted for other potential prognostic factors such as age at diagnosis.

Conclusion

Internationally consistent, population-wide data on cancer stage are essential for identifying differences between jurisdictions, and for tracking progress in improvements in diagnosis and stage-specific survival over time. Our results give the first population-wide picture of the distribution of incident cases and outcomes for childhood blood cancers in Australia stratified by extent of disease at diagnosis and thus provide a baseline for future comparisons. They also indicate possible areas for further investigation, including superior survival in AML and higher presenting stage in HL than reported elsewhere. It is hoped that more widespread implementation of the Toronto Guidelines will allow an international picture of stage-specific incidence and outcome that ultimately may inform better targeted control of these rare diseases.

Conflict of interest statement: The authors have no conflicts of interest to declare.

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TABLE 1 Summary of the Tier 2 staging systems in the Toronto Guidelines by type of blood cancer

Type of blood cancer ^a	Staging system	Stage category	Summary definition ^a
Acute lymphoblastic leukemia	COG	CNS1	No clinical signs of CNS involvement and no blasts in CSF.
		CNS2	No clinical signs of CNS involvement and blasts in CSF and either WBC<5µl CSF or WBC≥5µl CSF and RBC≥10µl CSF and Steinherz/Bleyer algorithm≤2.
		CNS3	Clinical signs of CNS involvement or blasts in CSF and WBC≥5µl CSF and either RBC<10µl CSF or RBC≥10µl CSF and Steinherz/Bleyer algorithm>2.
Acute myeloid leukemia	COG	CNS-	No clinical signs of CNS involvement and no blasts in CSF and non-traumatic lumbar puncture.
		CNS+	Clinical signs of CNS involvement or blasts in CSF or traumatic lumbar puncture.
Hodgkin lymphoma ^b	Ann Arbor ¹⁴	IA/IB	Involvement of either a single lymph node region or a single extra-lymphatic organ or site.
		IIA/IIB	Involvement of two or more lymph node regions on the same side of the diaphragm or localised involvement of a single extra-lymphatic organ/site with associated regional lymph node involvement.
		IIIA/IIIB	Involvement of two or more lymph node regions on opposite sides of the diaphragm.
		IVA/IVB	Diffuse or disseminated involvement of one or more extralymphatic organs; or isolated extra-lymphatic organ involvement in the absence of adjacent regional lymph node involvement but in conjunction with disease in distant sites; or any involvement of the liver, bone marrow, lungs (except by direct extension from another site) or CSF.
Non-Hodgkin lymphoma	St Jude/Murphy ¹⁵	I	Involvement of a single tumor mass or nodal area, excluding the abdomen and mediastinum.
		II	A single tumor (extranodal) with regional node involvement or two or more nodal areas or extranodal tumors on the same side of the diaphragm or a completely resected primary gastrointestinal tract tumor.
		III	Tumors (extranodal) or nodal areas on OPPOSITE sides of the diaphragm; or any primary intrathoracic tumors or extensive (unresectable) primary intra-abdominal disease or any paraspinal or epidural tumors regardless of other tumor sites.
		IV	Initial CNS and/or bone marrow involvement.

Abbreviations: CFS = cerebrospinal fluid; CNS = central nervous system; COG = Children's Oncology Group; RBC = red blood cells; WBC = white blood cells.

Notes:

a. For the full definitions, see <https://cancerqld.blob.core.windows.net/content/docs/childhood-cancer-staging-for-population-registries.pdf>.

b. The suffix "A" for HL stage indicates no constitutional symptoms while "B" indicates constitutional symptoms (including fevers, night sweats and/or weight loss).

TABLE 2 Characteristics of the study cohort by type of blood cancer, Australian Childhood Cancer Registry, 2006-2014

Type of blood cancer^a	n	Males (%)	Median age at diagnosis (years)	Deaths prior to 31 Dec 2015 (%)
Acute lymphoblastic leukemia	1,469	54.1	4	5.9
Acute myeloid leukemia	241	53.5	4	23.2
Hodgkin lymphoma	191	62.8	12	1.1
Non-Hodgkin lymphoma	301	74.8	8	10.0

Notes:

a. Classified according to the International Classification of Childhood Cancers, version 3 (ICCC-3).

TABLE 3 Five-year observed survival estimates for childhood blood cancers by stage, Australian Childhood Cancer Registry, 2006-2014^a

Type of blood cancer ^a	Tier 2 Stage ^b	n	Five-year observed survival estimate (%) ^c	p-value ^d
Acute lymphoblastic leukemia	CNS1	1,337	94.1 (92.5-95.4)	0.07
	CNS2	101	89.0 (79.4-94.2)	
	CNS3	31	90.3 (72.9-96.8)	
Acute myeloid leukemia	CNS-	158	77.4 (69.9-83.2)	0.94
	CNS+	83	77.7 (66.9-85.3)	
Hodgkin lymphoma	IA/IB	31	100.0	0.30
	IIA/IIB	67	100.0	
	IIIA/IIIB	38	97.1 (81.4-99.6)	
	IVA/IVB	55	100.0	
Non-Hodgkin lymphoma	I	36	97.2 (81.9-99.6)	0.22
	II	29	96.6 (78.0-99.5)	
	III	169	89.4 (83.4-93.3)	
	IV	67	85.2 (73.1-92.1)	

Abbreviations: CNS = central nervous system; n.a. = not applicable.

Notes:

a. Survival was followed up to 31 Dec 2015.

b. Type of cancer classified according to the International Classification of Childhood Cancers, version 3 (ICCC-3).¹

c. Stage was defined by the Toronto Paediatric Cancer Stage Guidelines.²

d. Values shown in brackets are the 95% confidence interval.

e. P-values were derived using a log-rank test.

FIGURE 1 Distribution of stage at diagnosis, Australia, 2006-2014, by A) acute lymphoblastic leukaemia; B) acute myeloid leukaemia; C) Hodgkin lymphoma; and D) non-Hodgkin lymphoma.

FIGURE 2 Kaplan-Meier survival curves, Australia, 2006-2014 , by A) acute lymphoblastic leukaemia; B) acute myeloid leukaemia; C) Hodgkin lymphoma; and D) non-Hodgkin lymphoma.