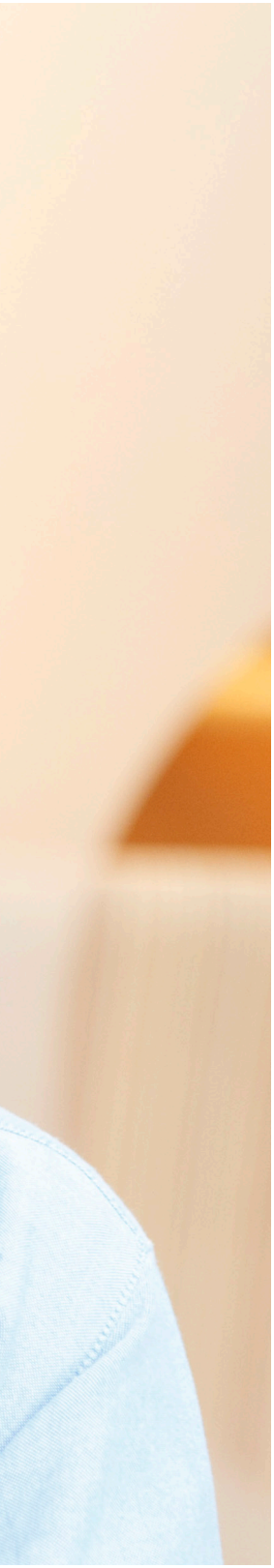
Photo by Tynan Studio

Johann Hitzler, MD, FRCPC, FAAP
Jacqueline Halton, MD, FRCPC
Jason D. Pole, PhD



6

Leukemia

Executive Summary

This chapter provides population-based information about the incidence of different forms of leukemia, the frequency of relapse, the use of hematopoietic stem cell transplantation (HSCT) and the probability of long term survival among children in Ontario diagnosed between 1985 and 2004.

Acute lymphoblastic leukemia (ALL) was the most common form of childhood leukemia (80.4% of all cases), followed by acute myeloid leukemia (AML) (15.6%). The age standardized incidence rate (ASIR) for any form of childhood leukemia was 44.4 cases per 1 million population per year (36.0 for ALL and 7.3 for AML). The incidence of leukemia was higher among males (56.0% of cases for ALL and 52.8% of cases for AML).

The age standardized mortality rate (ASMR) for any form of childhood leukemia was 10.7 deaths per 1 million population per year (6.4 for ALL and 3.6 for AML). Mortality rates were higher for males than females with ALL but were similar for AML. Mortality rates for leukemia decreased over time, particularly during the most recent reporting period (from 11.1 to 6.6 in 2000–2004). Mortality, expressed as the number of deaths per number of cases diagnosed, particularly improved for childhood AML (59.5% in 1990–1994, compared with 29.4% in 2000–2004), likely reflecting intensified chemotherapy and supportive care.

The proportions for event free survival (EFS) and overall survival were 0.71 and 0.81 for all children with leukemia diagnosed between 1995 and 2004. There was no significant difference between the 2 most recent treatment periods (1995–1999 and 2000–2004). As expected, EFS and overall survival were higher for children with ALL (0.77 and 0.87, respectively) than for AML (0.50 and 0.59, respectively). EFS after a diagnosis of ALL was lowest in infants (younger than 1 year of age; 0.37), intermediate for children 10 years or older (0.79) and highest in the age group 1–9 years (0.90). Stratified by risk group, the proportion of survival after 5 years among children with ALL was 0.95 for children with standard risk ALL and 0.82 for high risk ALL during the entire reporting period (1995–2004).

HSCT was a part of leukemia treatment for 18.7% of all children (45.8% of all patients with AML and 11.2% of those with ALL). Most recipients received stem cells from an allogeneic donor (97.4% during the most recent treatment period, 2000–2004). The majority of transplants for AML were carried out as part of a patient's initial treatment for leukemia (in first remission, 74.0%). In contrast, transplantation for ALL was most commonly used after a first relapse (in second remission, 59.6%). The probability of 5 year overall survival after allogeneic HSCT for children with any form of leukemia was 0.64; for ALL it was 0.66 and for AML, 0.68. The proportion of children treated for leukemia with a stem cell transplant decreased over time (from 22.2% to 14.9%) because there were fewer transplants for children with AML.

A relapse of leukemia developed in 21.0% of children (in 17.8% of those with ALL and 36.9% of those with AML). Relapse occurred more often in males than females. The proportion of children who relapsed decreased over time (by 24.7% for ALL and 30.0% for AML). Most (41.3%) relapses of ALL occurred late (more than 36 months after the initial diagnosis of leukemia) but early (within 18 months of initial diagnosis) in 71.0% of AML relapses. The proportion of children who survived at least 5 years after a relapse was significantly higher for ALL (0.58) than for AML (0.27).

Introduction

The term leukemia ("white blood" according to its etymology) encompasses the malignancies of the hematopoietic system, which present with disseminated involvement of blood and bone marrow. During childhood, leukemia is the most common form of cancer (31% of all new diagnoses of cancer[1]). Overall, it is a rare disease (48 new cases per year per 1 million population aged 0–14 years[1]).

Forms of childhood leukemia

There are 4 main types of leukemia affecting children. Acute lymphoblastic leukemia is by far the predominant form of childhood leukemia (approximately 80% of new cases[1]). ALL is subdivided according to the lymphoid lineage of the leukemic cell population (also termed blast cells) into B-precursor ALL (85% of ALL) and T-cell ALL (15% of ALL).[2] ALL occurs particularly frequently among young children and has a characteristic peak in its age distribution between 2 and 7 years.[3] Treatment consists of multi-agent chemotherapy administered mostly in the out-patient setting over approximately 2.5–3.5 years (longer in males). Prognosis depends on increasingly refined risk groups (see below); survival with current therapy ranges between 80% (high risk) and 90% (standard risk) for B-precursor ALL.

Acute myeloid leukemia is the second most common form of childhood leukemia (7 cases per 1 million population per year, or 15% of all new cases of leukemia per year[1]) and after a peak during the first year of life[4] it occurs with a constant incidence throughout childhood. Treatment consists of a series of highly intense multi-agent chemotherapy courses delivered in the in-patient setting over less than 6 months. Leukemic relapse and to a lesser degree treatment related mortality, mostly due to infections, result in long term survival rates of approximately 50–60%.[5-7]

Chronic myeloid leukemia (CML) is rare in children and more common in adults.[8] Prior to the introduction of tyrosine kinase inhibitors as a mechanism-specific treatment for CML, HSCT was the treatment of choice for pediatric patients. The role of HSCT in the treatment of children with CML is currently being redefined.[9]

Juvenile myelomonocytic leukemia (JMML) is a very rare type of leukemia found only in children.[10,11] HSCT currently is the only treatment associated with long term survival.[12,13]

Disease mechanisms

What causes childhood leukemia remains to be determined. Genome-wide analyses of leukemic blasts are defining the genetic mutations underlying ALL[14] and AML.[15,16] These mutations accumulate during a multi-step process and, by inducing increased cell proliferation, abnormal cell survival and impaired differentiation, result in the transformation of normal blood cells into the malignant cells that manifest as leukemia.[17] Strikingly, this process of leukemic transformation may be initiated before birth.[18,19] This was demonstrated by the detection of leukemia-specific fusion genes, for example ETV6-RUNX1 (TEL-AML1), in neonatal blood samples of children who years later developed leukemia, in this case B-precursor ALL. The observation that leukemic transformation is completed only in a small fraction of individuals in whom the process is initiated suggests that cooperating events are necessary; these may include environmental cues.[20]

Identification of specific acquired genetic abnormalities in leukemic blasts allows prognostic stratification of B-precursor ALL[21] and AML[22] and confirms the diagnosis in CML[8] and JMML.[10,11] Detection of the BCR-ABL1 fusion gene in CML, for example, and therapeutic inhibition of the encoded tyrosine kinase has established the feasibility of targeted chemotherapy and a new paradigm of drug development.

Leukemia is a disease that results from the accumulation of leukemic blasts that if left unchecked will interfere with normal organ function and survival. Based on seminal work in AML it is now clear that leukemic cell populations, although morphologically homogeneous, are functionally organized into a hierarchy.[23-25] Thus, a small fraction of leukemia-initiating cells (also termed cancer stem cells) within the leukemic cell population is capable of maintaining the malignant clone and must be eradicated to achieve long term cure.

Prognostic factors

Diagnostic investigation of childhood leukemia focuses on an increasingly refined set of prognostic criteria that allow the classification of a patient's leukemia as, for example, standard or high risk and determine the selection of the appropriate treatment intensity (e.g., lower vs. higher intensity chemotherapy protocols in ALL; chemotherapy vs. chemotherapy followed by HSCT in AML). Prognostic criteria in ALL include age, white blood cell count at diagnosis, lineage phenotype of the leukemic blasts and involvement of the central nervous system (CNS). Analysis of leukemic cells with cytogenetic (karyotype, fluorescence in situ hybridization) and molecular methods to detect fusion genes and specific gene mutations has refined the stratification of childhood leukemia into prognostic groups. It is anticipated that current genome-wide characterization of leukemic cells[14-16] will further expand and improve the prognostic algorithm.

In addition to the morphologic and genetic analysis of leukemic cells in the laboratory, the assessment of an individual patient's early response to treatment in his or her blood and bone marrow has proven prognostic. Initially, clearance of ALL cells in the blood of individual patients to either below or above a threshold level after 1 week of preliminary treatment (mainly with oral prednisone[26]) was used to select treatment intensity (higher intensity for those with slower clearance).

In the late 1990s, methods became available that allowed the detection of residual leukemia cells at the submicroscopic level, termed minimal residual disease (MRD),[27] in the bone marrow of children considered "in remission" (free of detectable leukemia) after the first 4 weeks of ALL treatment (i.e., the end of the induction phase). MRD assays detect either a pattern of cell surface markers or genetic, DNA-based markers that are uniquely present in an individual patient's leukemic cells. As few as 1 leukemic cell in 10,000 bone marrow cells can be detected by MRD testing, compared with 1 in 20 using standard microscopy. Thus, treatment can be intensified early on to maximize the probability of survival and decrease the risk of relapse for those patients whose MRD levels in the bone marrow remain high after the first treatment course. In AML, treatment response assessments after the first course of chemotherapy, initially by routine microscopy and recently by MRD testing, help determine which patients will require HSCT as part of their treatment. Conversely, patients with minimal or absent levels of MRD can expect a highly favourable prognosis and may be candidates for a reduction of treatment intensity.

Treatment

The intensity of treatment for childhood leukemia is stratified according to the estimated risk of leukemic relapse. Higher intensity treatment protocols, which are associated with more acute life threatening side effects (e.g., infection) and late effects (see below), are reserved for patients at high risk of relapse. Relapse of leukemia has a poor prognosis, with a probability of survival as low as 30–40%.[28-31] Treatment for leukemia in most cases consists of multi-agent chemotherapy. The use of cranial irradiation as CNS-directed therapy is increasingly avoided because of the development of significant late neurocognitive and endocrine effects in survivors and an increased risk of second malignancies (13.3% after 30 years), particularly malignant brain tumours, which may become apparent more than 25 years after treatment for leukemia.[32]

HSCT is used as part of the treatment for ultra high risk subsets of childhood leukemia patients during initial therapy (during first remission, CR1) and after a relapse (during second remission, CR2). HSCT allows the administration of anti-leukemic drug and irradiation doses that exceed the tolerance of the recipient's normal bone marrow, by subsequently supplying normal hematopoietic stem cells from a suitable donor. Long term survival rates after HSCT for ALL and AML are between 50% and 60%.[33,34]

There have been significant advances in leukemia treatment during the reporting period covered by this atlas. For childhood AML, a successful approach that includes intensified chemotherapy protocols and use of HSCT according to cytogenetic risk groups and early treatment response was pioneered by the United Kingdom Medical Research Council Study Group and has now been widely adopted.[6] In ALL, the use of a high intensity treatment element (delayed intensification therapy) was found to be beneficial for all risk groups.[26] Treatment for CML in children has been revolutionized with the introduction of oral tyrosine kinase inhibitors, which can achieve molecular remissions and have prompted an ongoing reassessment of the role of HSCT for this leukemia in childhood.[8]

The increased probability of long term survival for children with leukemia has brought the late adverse effects of leukemia treatment into focus. Lasting adverse neurocognitive late effects following cranial irradiation in subgroups of ALL, osteonecrosis in adolescents treated with high doses of glucocorticoids and cardiomyopathy, which may follow the use of anthracyclines during chemotherapy for both ALL and AML, serve as examples of the challenges facing survivors of childhood leukemia.[35,36] There is hope that the current era of genomic leukemia research and the new paradigm of chemotherapy targeting mechanisms, such as cell signaling pathways specific to leukemic cells, will not only enhance the efficacy of leukemia treatment, but also lower the frequency of lasting adverse effects.

Data collection

Monitoring progress requires basic data about how many children are affected per unit of population and year (incidence), the distribution of various forms of leukemia, the mortality rates associated with childhood leukemia, event free survival (time free of relapse, a second cancer or death) and overall survival after a diagnosis of leukemia. These data are essential for further analyses to identify the barriers to successful outcomes of leukemia treatment (e.g., leukemic relapse, treatment related mortality, late effects of treatment) and for effective policy decisions aimed at overcoming these barriers.

One principal source for these data is clinical trials conducted by large study groups such as the Children's Oncology Group, the Dana-Farber Cancer Institute Consortium and St. Jude Children's Research Hospital in North America, and European groups such as the Berlin-Frankfurt-Münster Study Group and the U.K. Medical Research Council Study Group. The strength of clinical trial data lies in the homogeneity of the underlying patient populations, as defined by study eligibility criteria and the use of uniform treatment protocols. Disadvantages are that trial-based data may not seamlessly cover a period of time if clinical studies accrued patients only during limited time intervals. Further, enrollment in clinical trials represents selected samples, which do not include patients who had leukemia but did not meet eligibility criteria, did not consent or did not complete the study.

A complementary data source is the population-based collection and analysis of information on childhood leukemia such as the one presented in the following discussion. Data captured on unselected cases in the entire population of children in a geographic area over a long period provide a valuable basis for the analysis of trends over time and the planning of resource allocation. As a trade-off, data collected in this fashion are influenced by differences in diagnostic and treatment approaches within and among participating centres. Population-based data collection may be broader but also limited to fewer items than clinical studies and may depend on linkage to other databases. The database that underlies the exhibits presented here, for example, does not completely capture out-of-hospital and late deaths before 1995 and therefore depends on linkage to other registries for the period 1985–1994. Thirty-six of 1,967 (1.8%) cases in the entire leukemia cohort did not link. As a result, estimates of overall survival and EFS were based on cohort members with a positive link (see Chapter 4: Survival).

The following exhibits provide a population-based perspective on the incidence of leukemia and associated mortality, the distribution of leukemia types, the use of HSCT, the incidence of leukemic relapse and survival for children in Ontario between 1985 and 2004.

Discussion

EXHIBIT 6.1a: **Age-standardized incidence rate and age-standardized mortality rate by period, age 0–14 years, in Ontario, 1985–2004**

			Total (1985–2004)					Year of diagnosis: 1985–1989				
			New cases	ASIR per million per year	Deaths	ASMR per million per year	Ratio ASMR / ASIR	New cases	ASIR per million per year	Deaths	ASMR per million per year	Ratio ASMR / ASIR
Total	**All leukemia**	**Overall**	**1967**	**44.43**	**467**	**10.67**	**0.24**	**414**	**41.12**	**136**	**13.46**	**0.33**
	Lymphoid	Overall	1582	35.78	278	6.39	0.18	348	34.54	95	9.40	0.27
	Acute myeloid	Overall	307	6.92	148	3.37	0.49	53	5.30	32	3.19	0.60
		APL	23	0.51	6	0.14	0.28	2	0.21	2	0.21	1.00
		Down	29	0.62	8	0.17	0.28	3	0.29	1	0.10	0.34
		Other	255	5.78	134	3.06	0.53	48	4.79	29	2.88	0.60
	Chronic myeloid	Overall	22	0.52	8	0.20	0.38	6	0.63	4	0.43	0.67
	JMML	Overall	18	0.38	13	0.28	0.73	3	0.27	3	0.27	1.00
	Leukemia NOS	Overall	38	0.83	20	0.43	0.52	4	0.38	2	0.18	0.47
Females	**All leukemia**	**Overall**	**877**	**19.8**	**198**	**4.49**	**0.23**	**184**	**18.34**	**55**	**5.38**	**0.29**
	Lymphoid	Overall	696	15.72	109	2.47	0.16	153	15.25	32	3.12	0.20
	Acute myeloid	Overall	145	3.26	69	1.57	0.48	24	2.40	18	1.78	0.74
		APL	14	0.32	3	0.08	0.24	2	0.21	2	0.21	1.00
		Down	9	0.19	2	0.04	0.22	0		0		
		Other	122	2.75	64	1.45	0.53	22	2.18	16	1.56	0.71
	Chronic myeloid	Overall	14	0.33	6	0.15	0.45	3	0.32	2	0.21	0.68
	JMML	Overall	4	0.09	4	0.09	1.00	1	0.09	1	0.09	1.00
	Leukemia NOS	Overall	18	0.40	10	0.22	0.54	3	0.29	2	0.18	0.61
Males	**All leukemia**	**Overall**	**1090**	**24.63**	**269**	**6.18**	**0.25**	**230**	**22.78**	**81**	**8.08**	**0.35**
	Lymphoid	Overall	886	20.06	169	3.92	0.20	195	19.30	63	6.28	0.33
	Acute myeloid	Overall	162	3.66	79	1.80	0.49	29	2.90	14	1.42	0.49
		APL	9	0.19	3	0.06	0.33					
		Down	20	0.43	6	0.13	0.30	3	0.29	1	0.10	0.34
		Other	133	3.04	70	1.61	0.53	26	2.61	13	1.32	0.51
	Chronic myeloid	Overall	8	0.19	2	0.05	0.27	3	0.32	2	0.21	0.67
	JMML	Overall	14	0.29	9	0.19	0.65	2	0.17	2	0.17	1.00
	Leukemia NOS	Overall	20	0.43	10	0.21	0.50	1	0.09	0		0.00

ASIR = age standardized incidence rate; ASMR = age standardized mortality rate; APL = acute promyelocytic leukemia; JMML = juvenile myelomonocytic leukemia; NOS = not otherwise specified; Down = Down syndrome

	1990–1994					1995–1999					2000–2004				
	New cases	ASIR per million per year	Deaths	ASMR per million per year	Ratio ASMR / ASIR	New cases	ASIR per million per year	Deaths	ASMR per million per year	Ratio ASMR / ASIR	New cases	ASIR per million per year	Deaths	ASMR per million per year	Ratio ASMR / ASIR
	494	**44.52**	**128**	**11.55**	**0.26**	**549**	**47.43**	**127**	**11.06**	**0.23**	**510**	**44.63**	**76**	**6.63**	**0.15**
	393	35.40	71	6.39	0.18	423	36.51	71	6.18	0.17	418	36.65	41	3.58	0.10
	86	7.79	51	4.63	0.60	100	8.69	45	3.93	0.45	68	5.90	20	1.74	0.29
	6	0.55	1	0.09	0.16	6	0.52	2	0.18	0.35	9	0.77	1	0.09	0.11
	13	1.09	4	0.34	0.31	7	0.58	1	0.08	0.14	6	0.52	2	0.17	0.33
	67	6.15	46	4.21	0.68	87	7.59	42	3.67	0.48	53	4.61	17	1.48	0.32
	7	0.68	2	0.20	0.30	4	0.35	1	0.08	0.24	5	0.42	1	0.09	0.21
	5	0.40	3	0.24	0.61	6	0.50	4	0.34	0.67	4	0.35	3	0.26	0.75
	3	0.26	1	0.08	0.31	16	1.38	6	0.52	0.38	15	1.31	11	0.96	0.74
	210	**18.93**	**56**	**5.00**	**0.26**	**260**	**22.43**	**55**	**4.80**	**0.21**	**223**	**19.49**	**32**	**2.78**	**0.14**
	171	15.39	35	3.11	0.20	196	16.84	28	2.42	0.14	176	15.40	14	1.21	0.08
	33	2.99	18	1.61	0.54	52	4.52	22	1.94	0.43	36	3.13	11	0.96	0.31
	2	0.20	0		0.00	4	0.35	1	0.10	0.27	6	0.51	0		0.00
	4	0.33	2	0.17	0.51	3	0.25	0		0.00	2	0.18	0		0.00
	27	2.45	16	1.44	0.59	45	3.92	21	1.84	0.47	28	2.44	11	0.96	0.39
	4	0.39	2	0.20	0.52	4	0.35	1	0.08	0.24	3	0.26	1	0.09	0.35
	0		0			2	0.17	2	0.17	1.00	1	0.09	1	0.09	1.00
	2	0.16	1	0.08	0.49	6	0.55	2	0.18	0.33	7	0.62	5	0.44	0.72
	284	**25.60**	**72**	**6.54**	**0.26**	**289**	**25.00**	**72**	**6.26**	**0.25**	**287**	**25.15**	**44**	**3.85**	**0.15**
	222	20.01	36	3.27	0.16	227	19.67	43	3.76	0.19	242	21.25	27	2.37	0.11
	53	4.80	33	3.03	0.63	48	4.17	23	1.99	0.48	32	2.77	9	0.78	0.28
	4	0.35	1	0.09	0.25	2	0.17	1	0.09	0.51	3	0.26	1	0.09	0.34
	9	0.76	2	0.17	0.22	4	0.33	1	0.08	0.25	4	0.35	2	0.17	0.50
	40	3.70	30	2.77	0.75	42	3.67	21	1.82	0.50	25	2.17	6	0.52	0.24
	3	0.29	0		0.00	0		0			2	0.17	0		0.00
	5	0.40	3	0.24	0.61	4	0.33	2	0.17	0.50	3	0.26	2	0.18	0.66
	1	0.10	0		0.00	10	0.83	4	0.34	0.41	8	0.69	6	0.52	0.75

Exhibit 6.1a

Incidence

A total of 1,967 children under 15 years of age were diagnosed with leukemia in Ontario between 1985 and 2004. Age standardized incidence rates are reported for 5 year intervals. Lymphoid leukemia, referred to in the following as acute lymphoblastic leukemia, accounted for the majority of cases (80.4%), followed by AML (15.5% of cases). All other forms of leukemia were rare (CML, 1.1%; JMML, 0.9%). A total of 38 cases (1.9% of the total) could not be further classified (leukemia not otherwise specified/NOS). Among children with AML, the proportions of those subgroups that are treated with distinct approaches were in keeping with reports based on clinical trials both for acute promyelocytic leukemia (APL, or French-American-British/FAB-M3, 9.8% vs. 7.5–9.0%[6]) and AML in children with Down syndrome (9.4% vs. 3.5–9.8%[37]). The higher incidence among males of ALL (56.0%) and AML (52.8%) was identical to the rate in recent trial-based reports.[2,6] The higher incidence of Down syndrome AML among males (69.0% vs. 48–52%[38]) and APL among females (60.9% vs. 45.6–59.5%[39]) was unexpected but is based on a small number of cases.

The ASIRs were 44.4 per 1 million population per year for any form of childhood leukemia, 35.8 for ALL and 6.9 for AML and were consistent with corresponding values (48, 38 and 7, respectively) reported for the age adjusted (ages 0–14 years) U.S. standard population (2000).[1]

Mortality

The ASMRs were 10.7 deaths per 1 million per year for any form of leukemia, 6.4 for ALL and 3.4 for AML from 1985 to 2004 based on the standard Ontario population (2001). To estimate the mortality among children diagnosed with leukemia, ratios of ASMR to ASIR were calculated.

Taking all forms of childhood leukemia together, the incidence of leukemia was approximately 4 times higher than the mortality from leukemia (ASMR/ASIR, 0.24).

The mortality/incidence ratio was lowest for ALL (0.18) and markedly higher for AML (0.49). The low ASMR/ASIR ratios for the prognostically favourable subsets APL (0.27), which is associated with a reported survival rate of 78.1%,[39] and AML in Down syndrome (0.28) were expected.[38]

Mortality expressed as the ASMR/ASIR ratio was lower in females with ALL (0.16) than in males (0.20), while no gender associated difference was observed for AML (0.49 in males, 0.48 in females), despite a larger number of males in the prognostically favourable subset of Down syndrome AML.

Mortality rates for leukemia NOS resembled those of AML more than those of ALL.

Trends

In a comparison of 5 year intervals, the incidence of all forms of childhood leukemia increased from 41.1 to 47.4 per 1 million between 1985 and 1999 before decreasing during the most recent reporting period (2000–2004) to 44.6, a value similar to that observed during 1990–1994 (44.5). The same pattern was observed for the ASIR of AML (an increase from 5.3 to 8.7 between 1985 and 1999 followed by a decrease to 5.9 during the most recent reporting period). In contrast, the ASIR of ALL increased from 34.5 to 36.7 from 1985 to 2004 and remained constant (36.5 and 36.7) during the 2 most recent reporting periods (1995–1999 and 2000–2004).

For all leukemia, mortality as measured by ASMR decreased over time. This decrease was gradual during 1985–1999 (from 13.5 to 11.1) and more accelerated during the most recent reporting period (11.1 to 6.6 between 2000 and 2004).

In relative terms, the ASMR decreased by 43.8% for ALL (from 6.4 to 3.6) and 62.4% for AML (from 4.6 to 1.8) between 1994 and 2004. The ratio of leukemia-associated mortality to incidence of leukemia (ASMR/ASIR) for ALL first decreased after 1989 (from 0.27 to 0.18), remained stable at this lower level until 1999 and then decreased further (to 0.10 for 2000–2004), reflecting improved survival. For AML the decrease began in 1995 and was both marked and sustained (from 0.60 in 1994 to 0.29 in 2004; decreasing by approximately 0.15 every 5 years), and illustrates the significant improvement of survival for children with AML since 1995.

Owing to methodologic limitations (see Chapter 4: Survival among Children Diagnosed with Cancer in Ontario from 1985 to 2004), longitudinal comparisons of ASMRs are most reliable after 1991. For both genders the ASMR for leukemia decreased by a similar degree (by 41.1% for males and 44.4% for females) between 1990 and 2004. Relative decreases in ASMRs in males were greater for AML (a 74.3% decrease) than for ALL (27.5%), whereas in females the ASMR showed a greater relative decrease for ALL (a 61.1% decrease) than for AML (40.4%). Available data showed no detectable improvement in ASMR over time for APL (FAB-M3) or Down syndrome AML, suggesting that the improved ASMR for AML occurred in the majority of AML patients who are not part of these specific prognostically favourable subsets.

EXHIBIT 6.1b: **Incidence and mortality by period for acute myeloid leukemia by French-American-British classification, age 0–14 years, in Ontario, 1985–2004**

			Total (1985–2004)				Year of diagnosis: 1985–1989			
			New cases		Deaths		New cases		Deaths	
			n	%	n	%	n	%	n	%
Total		Overall	**307**	**100.00**	**148**	**48.21**	**53**	**17.26**	**32**	**60.38**
	Non-Down acute myeloid leukemia	M0	9	2.93	6	66.67	0	0.00	0	
		M1	30	9.77	20	66.67	5	9.43	3	60.00
		M2	44	14.33	19	43.18	3	5.66	1	33.33
		APL	23	7.49	6	26.09	2	3.77	2	100.00
		M4	48	15.64	22	45.83	7	13.21	4	57.14
		M5	35	11.40	16	45.71	8	15.09	6	75.00
		M6	8	2.61	6	75.00	2	3.77	1	50.00
		M7	23	7.49	13	56.52	0	0.00	0	
		Unknown	58	18.89	32	55.17	23	43.40	14	60.87
	Down syndrome*		29	9.45	8	27.59	3	5.66	1	33.33

*72.4% (21/29) of the Down syndrome patients were M7.

Exhibit 6.1b

Based on a classification of AML according to blast morphology, the most common forms of childhood AML were myeloblastic (FAB-M2), myelo- and monoblastic (FAB-M4) and monoblastic (FAB-M5). Among children with Down syndrome, the predominant blast phenotype was megakaryoblastic (FAB-M7, 72.4%). These distributions are consistent with data collected in recent clinical trials.[6]

The mortality (expressed as number of deaths per number of cases diagnosed) due to childhood AML markedly decreased from 59.3% in 1990–1994 to 29.4% in 2000–2004. This trend highlights a significant improvement in AML therapy for children, which is likely the result of intensified chemotherapy[6] and supportive care. Compared with the mortality in the entire group of children with AML (48.2%), lower death rates, as expected, were observed for APL (FAB-M3, 26.1%) and Down syndrome AML (27.6%).[38,39] These data confirm the favourable prognosis and support the current use of distinct treatment approaches for these subtypes of AML.

During the most recent period (2000–2004) mortality proportions for all children with AML (29.4%) had decreased to those observed for these favourable subgroups over the entire reporting period (26.1% and 27.6% for APL and Down syndrome AML, respectively). In the latter sub-groups recent mortality (2000–2004) was lower for APL (11.1%) than for the entire reporting period (26.1%) but unchanged for Down syndrome AML (33.3% in 2000–2004 vs. 27.6% in 1985–2004). This observation may reflect the introduction of all-trans retinoic acid, improving management of acute hemorrhagic complications of APL, and at the same time may highlight room for further improvement in the treatment of Down syndrome AML.[40]

	1990–1994				1995–1999				2000–2004			
	New cases		Deaths		New cases		Deaths		New cases		Deaths	
	n	%	n	%	n	%	n	%	n	%	n	%
	86	**28.01**	**51**	**59.30**	**100**	**32.57**	**45**	**45.00**	**68**	**22.15**	**20**	**29.41**
	2	2.33	1	50.00	4	4.00	4	100.00	3	4.41	1	33.33
	11	12.79	9	81.82	10	10.00	5	50.00	4	5.88	3	75.00
	13	15.12	9	69.23	14	14.00	6	42.86	14	20.59	3	21.43
	6	6.98	1	16.67	6	6.00	2	33.33	9	13.24	1	11.11
	12	13.95	7	58.33	18	18.00	7	38.89	11	16.18	4	36.36
	5	5.81	4	80.00	12	12.00	3	25.00	10	14.71	3	30.00
	3	3.49	2	66.67	3	3.00	3	100.00	0	0.00	0	—
	7	8.14	7	100.00	10	10.00	6	60.00	6	8.82	0	0.00
	14	16.28	7	50.00	16	16.00	8	50.00	5	7.35	3	60.00
	13	15.12	4	30.77	7	7.00	1	14.29	6	8.82	2	33.33

EXHIBIT 6.2: **5 year overall and event free survival proportions by age group and period, age 0–14 years, in Ontario, 1985–2004**

			1985–2004		1995–2004				1985–1989	
	Age (years)	N	OSP	95% CI	OSP	95% CI	EFSP	95% CI	OSP	95% CI
All leukemia	**Overall**	**1967**	**0.79**	**0.77-0.80**	**0.81**	**0.78-0.83**	**0.71**	**0.69-0.74**	**0.72**	**0.64-0.79**
	< 1	94	0.37	0.26-0.47	0.40	0.28-0.53	0.35	0.23-0.47	0.21	0.06-0.42
	1–4	790	0.84	0.81-0.86	0.85	0.82-0.88	0.75	0.70-0.78	0.82	0.72-0.88
	5–9	730	0.83	0.79-0.85	0.85	0.81-0.88	0.76	0.72-0.80	0.75	0.55-0.87
	10–14	353	0.69	0.64-0.74	0.72	0.65-0.77	0.62	0.54-0.68	0.69	0.57-0.79
Lymphoid	**Overall**	**1582**	**0.85**	**0.83-0.87**	**0.87**	**0.85-0.89**	**0.77**	**0.75-0.80**	**0.78**	**0.68-0.86**
	< 1	47	0.38	0.24-0.52	0.37	0.20-0.54	0.32	0.17-0.49	0.28	0.05-0.57
	1–4	659	0.90	0.87-0.92	0.91	0.88-0.94	0.80	0.76-0.84	0.87	0.77-0.93
	5–9	630	0.87	0.83-0.89	0.90	0.86-0.92	0.81	0.76-0.84	0.79	0.52-0.92
	10–14	246	0.78	0.72-0.83	0.79	0.71-0.85	0.70	0.62-0.77	0.75	0.60-0.85
Acute myeloid	**Overall**	**307**	**0.52**	**0.46-0.57**	**0.59**	**0.52-0.66**	**0.50**	**0.43-0.57**	**0.42**	**0.26-0.57**
	< 1	32	0.39	0.22-0.56	0.54	0.29-0.73	0.48	0.25-0.67	0.28	0.03-0.64
	1–4	107	0.55	0.45-0.64	0.62	0.49-0.73	0.52	0.40-0.64		
	5–9	83	0.55	0.43-0.66	0.58	0.44-0.69	0.52	0.38-0.64	0.49	0.13-0.78
	10–14	85	0.47	0.36-0.58	0.56	0.40-0.69	0.43	0.29-0.57	0.48	0.23-0.70
Chronic myeloid	**Overall**	**22**	**0.77**	**0.51-0.91**	**0.72**	**0.29-0.92**	**0.56**	**0.24-0.79**	**1.00**	
	< 1	0								
	1–4	3	0.67	0.05-0.95	0.51	0.00-0.92	0.51	0.00-0.92		
	5–9	6	1.00		1.00		1.00			
	10–14	13	0.66	0.29-0.87	0.77	0.25-0.95	0.53	0.14-0.81	1.00	
JMML	**Overall**	**18**	**0.24**	**0.08-0.45**	**0.27**	**0.08-0.50**	**0.20**	**0.05-0.43**		
	< 1	12	0.38	0.12-0.64	0.37	0.11-0.64	0.27	0.06-0.55		
	1–4	5								
	5–9	1								
	10–14	0								
Leukemia NOS	**Overall**	**38**	**0.54**	**0.37-0.69**	**0.56**	**0.36-0.72**	**0.44**	**0.26-0.60**	**0.27**	**0.01-0.68**
	< 1	3								
	1–4	16	0.68	0.39-0.85	0.68	0.36-0.86	0.49	0.22-0.71		
	5–9	10	0.52	0.16-0.79	0.44	0.10-0.74	0.44	0.10-0.75	1.00	
	10–14	9	0.52	0.17-0.78	0.52	0.17-0.78	0.37	0.09-0.66		

If blank, number is not estimable.
OSP = overall survival proportion; CI = confidence interval; EFSP = event free survival proportion; JMML = juvenile myelomonocytic leukemia; NOS = not otherwise specified
*Although OSP is reported as lower than EFSP, it is an artifact of the small sample size.

1990–1994		1995–1999				2000–2004			
OSP	95% CI	OSP	95% CI	EFSP	95% CI	OSP	95% CI	EFSP	95% CI
0.77	**0.73-0.80**	**0.78**	**0.74-0.81**	**0.68**	**0.64-0.72**	**0.84**	**0.81-0.87**	**0.75**	**0.71-0.78**
0.39	0.18-0.60	0.40	0.24-0.55	0.31	0.17-0.46	0.42	0.22-0.61	0.40	0.20-0.59
0.82	0.76-0.86	0.81	0.76-0.85	0.73	0.67-0.78	0.90	0.85-0.93	0.76	0.70-0.81
0.79	0.72-0.84	0.83	0.77-0.87	0.71	0.65-0.77	0.87	0.81-0.90	0.82	0.76-0.86
0.69	0.59-0.78	0.69	0.59-0.77	0.59	0.49-0.68	0.75	0.65-0.82	0.64	0.54-0.72
0.84	**0.80-0.87**	**0.85**	**0.81-0.88**	**0.75**	**0.71-0.79**	**0.89**	**0.86-0.92**	**0.79**	**0.76-0.83**
0.49	0.20-0.73	0.39	0.19-0.59	0.28	0.12-0.47	0.35	0.10-0.61	0.39	0.12-0.67*
0.89	0.83-0.92	0.88	0.83-0.92	0.81	0.75-0.86	0.94	0.89-0.97	0.79	0.73-0.84
0.81	0.75-0.87	0.89	0.83-0.93	0.76	0.69-0.82	0.90	0.85-0.93	0.85	0.79-0.89
0.83	0.71-0.90	0.77	0.65-0.85	0.69	0.58-0.79	0.81	0.70-0.89	0.71	0.59-0.80
0.40	**0.29-0.50**	**0.53**	**0.44-0.62**	**0.45**	**0.36-0.54**	**0.67**	**0.56-0.76**	**0.56**	**0.45-0.66**
0.19	0.01-0.53	0.49	0.18-0.74	0.49	0.18-0.74	0.65	0.28-0.87	0.40	0.08-0.72
0.44	0.27-0.60	0.60	0.43-0.73	0.52	0.36-0.66	0.65	0.42-0.81	0.53	0.33-0.70
0.53	0.26-0.75	0.47	0.32-0.60	0.40	0.25-0.55	0.69	0.46-0.84	0.66	0.42-0.82
0.30	0.14-0.48	0.48	0.27-0.66	0.35	0.18-0.54	0.64	0.42-0.80	0.51	0.31-0.68
0.74	**0.28-0.93**	**0.57**	**0.12-0.86**	**0.39**	**0.10-0.68**	**1.00**		**1.00**	
		0.51	0.00-0.92	0.51	0.00-0.92	0.64	0.42-0.80	0.51	0.31-0.68
1.00		0.51	0.00-0.92	0.51	0.00-0.92				
0.43	0.06-0.78	0.68	0.12-0.93	0.37	0.06-0.70	1.00		1.00	
		0.24	**0.04-0.53**	**0.12**	**0.01-0.41**	**0.25**	**0.04-0.55**	**0.22**	**0.04-0.50**
		0.48	0.07-0.82	0.25	0.01-0.65	0.29	0.04-0.63	0.28	0.05-0.59
0.66	**0.06-0.94**	**0.65**	**0.35-0.84**	**0.48**	**0.21-0.71**	**0.43**	**0.21-0.64**	**0.35**	**0.16-0.55**
0.50	0.01-0.91	0.77	0.32-0.94	0.39	0.04-0.75	0.48	0.18-0.73	0.39	0.16-0.62
1.00		0.53	0.11-0.83	0.59	0.13-0.88*	0.21	0.00-0.75	0.21	0.00-0.75
		1.00		1.00		0.45	0.11-0.74	0.28	0.05-0.59

Exhibit 6.2

The proportions of 5 year EFS and overall survival for all children with leukemia were 0.71 and 0.81, respectively, between 1995 and 2004. There was no significant difference between the 2 most recent treatment periods (1995–1999 and 2000–2004). Both EFS and overall survival were higher for children with ALL (0.77 and 0.87, respectively) than for those with AML (0.50 and 0.59, respectively) and were within the range reported by clinical trials.[2,6,7,41,42] The proportion of overall survival for children with any leukemia, ALL and AML, which was calculated after including linkage-based mortality data for out-of-hospital and late deaths between 1985 and 1994, was similar to results based only on directly captured mortality data (1995–2004).

Age at diagnosis has a significant impact on the prognosis of ALL.[43] EFS was lowest in infants with ALL (younger than 1 year of age; EFS proportion, 0.37), intermediate for children 10 years or older (0.79) and highest in the age group 1–9 years (0.90). The same pattern applied to overall survival (0.37 for infants less than 1 year of age; 0.79 for children 10 years or older; 0.90 for the most favourable age group, 1–9 years). These results are as expected and reflect a widespread risk classification of childhood ALL.[43] Whereas all children 10 or older are considered to have high risk ALL by virtue of their age alone, not all children in the 1–9 year age group are expected to have standard risk ALL – some would be classified as having high risk ALL if their white blood cell count at diagnosis was 50 × 10^9/L or more. In contrast, EFS and overall survival of children with AML was not significantly different among age groups, consistent with data reported by clinical study groups.[5,6]

EXHIBIT 6.3: **Hematopoietic stem cell transplantation by relapse status and period, age 0–14 years, in Ontario, 1995–2004**

	1995–2004							1995–1999		
		HSCT			Timing of HSCT (%)				HSCT	
	Total patients	n	%	Allogeneic (%)	CR1	CR2	CR3	Total patients	n	%
All leukemia	**1059**	**198**	**18.70**	**86.36**	**54.55**	**38.89**	**6.57**	**549**	**122**	**22.22**
Lymphoid	841	94	11.18	100.00	27.66	59.57	12.77	423	52	12.29
Acute myeloid	168	77	45.83	64.94	74.03	25.97	0.00	100	58	58.00
Chronic myeloid	9	6	66.67	100.00	100.00	0.00	0.00	4	3	75.00
JMML	10	5	50.00	100.00	100.00	0.00	0.00	6	2	33.33
Leukemia NOS	31	16	51.61	100.00	87.50	6.25	6.25	16	7	43.75

HSCT = hematopoietic stem cell transplantation; CR1 = first remission (prior to relapse); CR2 = second remission (after first relapse); CR3 = third remission (after second relapse); JMML = juvenile myelomonocytic leukemia; NOS = not otherwise specified

Infants (less than 1 year of age) with ALL had consistently worse EFS and overall survival than other age groups in both periods (1995–1999 and 2000–2004). No other significant age-based differences were apparent in EFS or overall survival in children with ALL and AML over time. EFS (0.44) and overall survival (0.56) for leukemia NOS resembled more closely the proportions for AML than for ALL, without significant differences among age groups or treatment periods.

CML and JMML are rare forms of childhood leukemia and in this cohort accounted for 1.1% of cases (compared with the 3% expected[8]) and 0.9% of cases (compared with the 2–3% expected[12]), respectively. JMML is found predominantly in young children – half of all patients are diagnosed before 2 years of age[11,44] – and long term cure requires HSCT. The observed 5 year EFS (0.20) and overall survival (0.27) proportions were lower than reported for larger series (EFS 49–55% and overall survival 57.9%[12,13]) and likely result from the small number of cases analyzed. Treatment for CML has undergone a significant transformation since the use of oral tyrosine kinase inhibitors began to decrease the use of HSCT.[8] A first phase I study of imatinib in pediatric patients with Philadelphia chromosome positive leukemia was reported in 2004.[45] The EFS (0.56) and overall survival (0.72) observed between 1995 and 2004 are therefore likely to change significantly during future treatment periods.

				2000–2004						
	Timing of HSCT (%)				HSCT			Timing of HSCT (%)		
Allogeneic (%)	CR1	CR2	CR3	Total patients	n	%	Allogeneic (%)	CR1	CR2	CR3
79.51	**59.02**	**35.25**	**5.74**	**510**	**76**	**14.90**	**97.37**	**47.37**	**46.05**	**6.58**
100.00	30.77	55.77	13.46	418	42	10.05	100.00	23.81	64.29	11.90
56.90	77.59	22.41	0.00	68	19	27.94	89.47	63.16	36.84	0.00
100.00	100.00	0.00	0.00	5	3	60.00	100.00	100.00	0.00	0.00
100.00	100.00	0.00	0.00	4	3	75.00	100.00	100.00	0.00	0.00
100.00	85.71	14.29	0.00	15	9	60.00	100.00	88.89	11.11	0.00

Exhibit 6.3

Among 1,059 children with leukemia, 18.7% underwent HSCT between 1995 and 2004. They included 45.8% of all patients with AML and 11.2% of all patients with ALL. Because of the higher overall number of patients with ALL, the largest number of HSCT procedures was carried out for ALL (47.4% of all transplants, compared with 38.9% for AML). The majority of transplant recipients received allogeneic grafts (86.3%). Non-allogeneic grafts were used only for a subset of AML patients (35.1%). The majority of transplants for AML were carried out as part of the initial treatment for leukemia (in first remission; 74.0% of transplants for AML). In contrast, transplantation in second remission (after a first relapse) was the most common indication in children with ALL (59.6% of transplants for ALL). These findings are consistent with the current use of HSCT in the treatment of childhood leukemia.

From the earlier (1995–1999) to the more recent (2000–2004) period the proportion of patients undergoing HSCT as part of leukemia treatment decreased from 22.2% to 14.9%. This decrease was accounted for largely by a lower proportion of children with AML (27.9% vs. 58.0% during the earlier period), whereas the proportion of patients with ALL remained similar (12.2% in 1995–1999 and 10.0% in 2000–2004). The use of allogeneic donors for AML patients increased over time (from 56.9% to 89.5%), raising the overall proportion of allogeneic transplants from 79.5% to 97.4%.

Among children with AML, HSCT was not only used less frequently during the recent treatment period but also less frequently during first remission (i.e., as part of initial leukemia therapy) than before (63.1% vs. 77.6% of AML). Fewer HSCT procedures in first remission were also observed for ALL (23.8% vs. 30.8%). Possible explanations include refined risk stratification (by cytogenetics and treatment response) and improved treatment outcomes after chemotherapy.

EXHIBIT 6.4: **5 year overall survival proportion from diagnosis among children who received hematopoietic stem cell transplantation by period, age 0–14 years, in Ontario, 1995–2004**

		1995–2004				1995–1999				2000–2004			
		Received HSCT				Received HSCT				Received HSCT			
HSCT type	Diagnosis	Total patients	n	OSP	95% CI	Total patients	n	%	95% CI	Total patients	n	%	95% CI
All	**All leukemia**	**1059**	**198**	**0.63**	**0.55-0.70**	**549**	**122**	**0.66**	**0.55-0.76**	**510**	**76**	**0.62**	**0.52-0.71**
	Lymphoid	841	94	0.66	0.53-0.75	423	52	0.76	0.56-0.88	418	42	0.61	0.47-0.72
	Acute myeloid	168	77	0.64	0.52-0.74	100	58	0.62	0.47-0.74	68	19	0.76	0.58-0.87
	Chronic myeloid	9	6	1.00		4	3	1.00		5	3	1.00	
	JMML	10	5	0.30	0.03-0.66	6	2			4	3	0.22	0.00-0.73
	Leukemia NOS	31	16	0.37	0.14-0.61	16	7			15	9	0.32	0.10-0.58
Allogeneic	**All leukemia**		**171**	**0.64**	**0.55-0.71**		**97**	**0.69**	**0.55-0.80**		**74**	**0.61**	**0.51-0.70**
	Lymphoid		94	0.66	0.53-0.75		52	0.76	0.56-0.88		42	0.61	0.47-0.72
	Acute myeloid		50	0.68	0.52-0.80		33	0.68	0.47-0.83		17	0.75	0.55-0.87
	Chronic myeloid		6	1.00			3	1.00			3	1.00	
	JMML		5	0.30	0.03-0.66		2				3	0.22	0.00-0.73
	Leukemia NOS		16	0.37	0.14-0.61		7				9	0.32	0.10-0.58
Autologous	**All leukemia**		**27**	**0.56**	**0.36-0.72**		**25**	**0.56**	**0.35-0.73**		**2**	**0.78**	**0.35-0.95**
	Lymphoid		0				0				0		
	Acute myeloid		27	0.56	0.36-0.72		25	0.56	0.35-0.73		2	0.78	0.35-0.95
	Chronic myeloid		0				0				0		
	JMML		0				0				0		
	Leukemia NOS		0				0				0		

If blank, number is not estimable.
HSCT = hematopoietic stem cell transplantation; OSP = overall survival proportion; CI = confidence interval; JMML = juvenile myelomonocytic leukemia; NOS = not otherwise specified

Exhibit 6.4

For the entire period (1995–2004) the proportion of 5 year overall survival after allogeneic HSCT for all forms of pediatric leukemia was 0.64; for ALL it was 0.66 and for AML, 0.68. Autologous transplantation, which was confined to AML, resulted in an overall survival of 0.56. While the frequency of non-allogeneic HSCT markedly decreased during the most recent treatment period (see also Exhibit 6.3), no significant change in overall survival after HSCT over time was apparent.

EXHIBIT 6.5: **Leukemia relapse according to interval from initial diagnosis, by period, age 0–14 years, in Ontario, 1995–2004**

		1995–2004					
		Relapse			Time to relapse in months from diagnosis (%)		
		Total (n)	Yes				
			n	%	0–17	18–35	36+
All	**All leukemia**	**1059**	**222**	**20.96**	**42.34**	**25.23**	**32.43**
	Lymphoid	841	150	17.84	29.33	29.33	41.33
	Acute myeloid	168	62	36.90	70.97	17.74	11.29
	Chronic myeloid	9	1	11.11	0.00	0.00	100.00
	JMML	10	1	10.00	100.00	0.00	0.00
	Leukemia NOS	31	8	25.81	62.50	12.50	25.00
Females	**All leukemia**	**483**	**88**	**18.22**	**46.59**	**19.32**	**34.09**
	Lymphoid	372	56	15.05	30.36	25.00	44.64
	Acute myeloid	88	29	32.95	82.76	6.90	10.34
	Chronic myeloid	7	1	14.29	0.00	0.00	100.00
	JMML	3	0	0.00			
	Leukemia NOS	13	2	15.38	0.00	50.00	50.00
Males	**All leukemia**	**575**	**133**	**23.13**	**39.10**	**29.32**	**31.58**
	Lymphoid	469	94	20.04	28.72	31.91	39.36
	Acute myeloid	80	33	41.25	60.61	27.27	12.12
	Chronic myeloid	2	0	0.00			
	JMML	7	1	14.29	100.00	0.00	0.00
	Leukemia NOS	18	6	33.33	83.33	0.00	16.67

JMML = juvenile myelomonocytic leukemia; NOS = not otherwise specified

Exhibit 6.5

The prognosis for survival after a relapse of leukemia depends mainly on 2 prognostic factors: the time between initial diagnosis of leukemia and relapse (see Exhibit 6.5) and the site of relapse (see Exhibit 6.6).

Between 1995 and 2004 a relapse of leukemia developed in 21.0% of children with leukemia (including 17.8% of those with ALL and 36.9% of those with AML). Males had a higher proportion of cases with relapse (23.2% of males had a relapse of leukemia, 20.0% a relapse of ALL and 41.3% a relapse of AML) than did females (18.2% of females with leukemia had a relapse, 15.1% a relapse of ALL and 33.0% a relapse of AML), in keeping with trial-based results.[30,31] There was a marked decrease in the proportion of children who relapsed between the earlier period (1995–1999) and the more recent period (2000–2004). The proportion of children who relapsed decreased for any leukemia from 24.4% to 17.3% (a 29.1% decrease), for ALL from 20.3% to 15.3% (a 24.6% decrease) and for AML from 42.0% to 29.4% (a 30.0% decrease). The decrease was larger among females (36.5%; from 21.9% to 13.9%) than males (25.2%; from 26.6% to 19.9%) and slightly larger for AML than ALL.

In ALL, a late relapse, defined as occurring more than 36 months after initial diagnosis of leukemia, is more favourable than an early relapse (18–35 months from diagnosis). Very early relapse (within 18 months of initial diagnosis) has the least favourable prognosis.[28–31,46] For AML, relapse occurring more than 1 year after initial diagnosis is considered more favourable than relapse prior to this point.[47,48]

1995–1999						2000–2004					
Relapse			Time to relapse in months from diagnosis (%)			Relapse			Time to relapse in months from diagnosis (%)		
Total (n)	Yes					Total (n)	Yes				
	n	%	0–17	18–35	36+		n	%	0–17	18–35	36+
549	**134**	**24.41**	**40.30**	**24.63**	**35.07**	**510**	**88**	**17.25**	**45.45**	**26.14**	**28.41**
423	86	20.33	24.42	26.74	48.84	418	64	15.31	35.94	32.81	31.25
100	42	42.00	71.43	21.43	7.14	68	20	29.41	70.00	10.00	20.00
4	1	25.00	0.00	0.00	100.00	5	0	0.00			
6	0	0.00				4	1	25.00	100.00	0.00	0.00
16	5	31.25	60.00	20.00	20.00	15	3	20.00	66.67	0.00	33.33
260	**57**	**21.92**	**47.37**	**17.54**	**35.09**	**223**	**31**	**13.90**	**45.16**	**22.58**	**32.26**
196	35	17.86	28.57	22.86	48.57	176	21	11.93	33.33	28.57	38.10
52	20	38.46	85.00	5.00	10.00	36	9	25.00	77.78	11.11	11.11
4	1	25.00	0.00	0.00	100.00	3	0	0.00			
2	0	0.00				1	0	0.00			
6	1	16.67	0.00	100.00	0.00	7	1	14.29	0.00	0.00	100.00
289	**77**	**26.64**	**35.06**	**29.87**	**35.06**	**287**	**57**	**19.86**	**45.61**	**28.07**	**26.32**
227	51	22.47	21.57	29.41	49.02	242	43	17.77	37.21	34.88	27.91
48	22	45.83	59.09	36.36	4.55	32	11	34.38	63.64	9.09	27.27
0	0					2	0	0.00			
4	0	0.00				3	1	33.33	100.00	0.00	0.00
10	4	40.00	75.00	0.00	25.00	8	2	25.00	100.00	0.00	0.00

Using this grouping based on time to relapse, the majority of relapses in children with ALL occurred late (41.3%). In contrast, relapses in AML occurred predominantly within the first 18 months after diagnosis (71.0%). This pattern applied to both males and females in the entire cohort (1995–2004). Over time – that is, comparing the periods 1995–1999 and 2000–2004 – late relapse of ALL (more than 36 months from diagnosis) and relapse of AML less than 18 months from diagnosis remained the most common forms of relapse among females, while their overall relapse rates markedly decreased. Among males with ALL, however, the proportion of (prognostically favourable) late relapse decreased while (prognostically unfavourable) very early relapse increased (from 21.6% to 37.2%).

The proportion of AML relapses was lower in females than in males and decreased in both over time. AML relapse within the first 18 months from diagnosis, however, accounted for a larger share of relapse cases among females than males during both time periods. This suggests that relapse of AML in females overall was less frequent but of a higher risk type when it did occur.

Lower relapse rates for ALL in females than in males have been observed consistently.[30,31] Although the overall decrease of ALL relapse during the recent treatment period occurred in parallel with improvements in the risk stratification and intensification of ALL therapy, it is not possible to deduce specific causes of this trend.

EXHIBIT 6.6a: **Leukemia relapse according to site of relapse by period, ages 0–14 years, Ontario, 1995–2004**

	1995–2004								1995–1999		
		Relapse		Relapse site (%)						Relapse	
	Total patients	n	%	Bone marrow only	Isolated CNS	Testes	Bone marrow and CNS or testes	Other	Total patients	n	%
Percentage for relapse site based on those who relapsed											
All leukemia	**1059**	**222**	**20.96**	**71.17**	**14.41**	**3.60**	**6.76**	**4.05**	**549**	**134**	**24.41**
Lymphoid	841	150	17.84	62.00	20.67	5.33	8.67	3.33	423	86	20.33
Acute myeloid	168	62	36.90	91.94	1.61	0.00	1.61	4.84	100	42	42.00
Chronic myeloid	9	1	11.11	100.00	0.00	0.00	0.00	0.00	4	1	25.00
JMML	10	1	10.00	100.00	0.00	0.00	0.00	0.00	6	0	0.00
Leukemia NOS	31	8	25.81	75.00	0.00	0.00	12.50	12.50	16	5	31.25
Percentage for relapse site based on total patients											
All leukemia	**1059**	**222**	**20.96**	**14.92**	**3.02**	**0.76**	**1.42**	**0.85**	**549**	**134**	**24.41**
Lymphoid	841	150	17.84	11.06	3.69	0.95	1.55	0.59	423	86	20.33
Acute myeloid	168	62	36.90	33.93	0.60	0.00	0.60	1.79	100	42	42.00
Chronic myeloid	9	1	11.11	11.11	0.00	0.00	0.00	0.00	4	1	25.00
JMML	10	1	10.00	10.00	0.00	0.00	0.00	0.00	6	0	0.00
Leukemia NOS	31	8	25.81	19.35	0.00	0.00	3.23	3.23	16	5	31.25

CNS = central nervous system; JMML = juvenile myelomonocytic leukemia; NOS = not otherwise specified

Exhibit 6.6a

Leukemic relapse may occur in the bone marrow, outside the bone marrow (such as in the central nervous system, testes or, less frequently, other organs) or both. The majority of relapsed ALL involved the bone marrow as the only site (62.0%), followed by isolated involvement of the CNS (20.7%) and testicular tissue (5.3%). These observations are consistent with data derived from clinical trials for relapse of childhood ALL.[31]

In AML the predominance of relapse in the bone marrow was even more pronounced (91.9% bone marrow alone and 93.6% for bone marrow combined with other sites, vs. reported proportions of 79.4% for bone marrow alone and 89.2% for bone marrow combined with other sites[47]). The distribution of sites of leukemic relapse in children is in keeping with available reports and appeared stable for both ALL and AML during the 2 reporting periods (1995–1999 and 2000–2004).

2000–2004												
Relapse site (%)						Relapse			Relapse site (%)			
Bone marrow only	Isolated CNS	Testes	Bone marrow and CNS or testes	Other	Total patients	n	%	Bone marrow only	Isolated CNS	Testes	Bone marrow and CNS or testes	Other
74.63	**12.69**	**3.73**	**6.72**	**2.24**	**510**	**88**	**17.25**	**65.91**	**17.05**	**3.41**	**6.82**	**6.82**
63.95	18.60	5.81	9.30	2.33	418	64	15.31	59.38	23.44	4.69	7.81	4.69
95.24	2.38	0.00	0.00	2.38	68	20	29.41	85.00	0.00	0.00	5.00	10.00
100.00	0.00	0.00	0.00	0.00	5	0	0.00					
					4	1	25.00	100.00	0.00	0.00	0.00	0.00
80.00	0.00	0.00	20.00	0.00	15	3	20.00	66.67	0.00	0.00	0.00	33.33
18.21	**3.10**	**0.91**	**1.64**	**0.55**	**510**	**88**	**17.25**	**11.37**	**2.94**	**0.59**	**1.18**	**1.18**
13.00	3.78	1.18	1.89	0.47	418	64	15.31	9.09	3.59	0.72	1.20	0.72
40.00	1.00	0.00	0.00	1.00	68	20	29.41	25.00	0.00	0.00	1.47	2.94
25.00	0.00	0.00	0.00	0.00	5	0	0.00	0.00	0.00	0.00	0.00	0.00
0.00	0.00	0.00	0.00	0.00	4	1	25.00	25.00	0.00	0.00	0.00	0.00
25.00	0.00	0.00	6.25	0.00	15	3	20.00	13.33	0.00	0.00	0.00	6.67

EXHIBIT 6.6b: **5 year overall survival proportions by relapse status and period, age 0–14 years, in Ontario, 1995–2004**

Diagnosis	1995–2004							1995–1999			
	Total patients	Relapse			No relapse			Total patients	Relapse		
		n	OSP	95% CI	n	OSP	95% CI		n	OSP	95% CI
All leukemia	**1059**	**222**	**0.48**	**0.41-0.56**	**837**	**0.91**	**0.89-0.93**	**549**	**134**	**0.50**	**0.39-0.60**
Lymphoid	841	150	0.58	0.48-0.66	691	0.95	0.93-0.97	423	86	0.63	0.48-0.75
Acute myeloid	168	62	0.27	0.16-0.39	106	0.80	0.71-0.87	100	42	0.26	0.14-0.40
Chronic myeloid	9	1	1.00		8	0.87	0.35-0.98	4	1		
JMML	10	1			9	0.29	0.05-0.60	6	0		
Leukemia NOS	31	8	0.39	0.09-0.70	23	0.61	0.36-0.78	16	5	0.38	0.03-0.76

If blank, number is not estimable.
OSP = overall survival proportion; CI = confidence interval; JMML = juvenile myelomonocytic leukemia; NOS = not otherwise specified

Exhibit 6.6b

The proportion of children who survived at least 5 years was significantly higher after a relapse of ALL (0.58) than after a relapse of AML (0.27). Among patients who did not experience a leukemic relapse, a higher proportion of those with ALL survived (0.95) than of those with AML (0.80). This observation is consistent with the higher mortality associated with AML therapy, likely resulting from the use of more intense chemotherapy protocols and the more frequent use of HSCT. This pattern remained stable during the 2 reporting periods (1995–1999 and 2000–2004).

While the 5 year overall survival proportion was significantly lower for children with relapsed AML during the early treatment period, this difference was not apparent during the more recent period. Possible explanations lie in improvements in survival for children with relapsed AML – for example, due to improved indications and outcomes for first or second HSCT.

			2000–2004						
No relapse			Total patients	Relapse			No relapse		
n	OSP	95% CI		n	OSP	95% CI	n	OSP	95% CI
415	**0.89**	**0.85-0.92**	**510**	**88**	**0.50**	**0.41-0.59**	**422**	**0.92**	**0.90-0.95**
337	0.93	0.87-0.96	418	64	0.57	0.46-0.66	354	0.96	0.94-0.98
58	0.79	0.66-0.88	68	20	0.35	0.18-0.52	48	0.82	0.68-0.90
3	0.67	0.05-0.95	5	0			5	1.00	
6			4	1			3	0.28	0.05-0.59
11	0.76	0.34-0.94	15	3	0.47	0.00-0.91	12	0.45	0.20-0.67

EXHIBIT 6.7: **5 year overall survival proportions for lymphoid leukemia patients by risk group and period, age 0–14 years, in Ontario, 1995–2004**

	5 year survival proportion by risk group								
	1995–2004						1995–1999		
Age (years)	Standard			High			Standard		
	n	OSP	95% CI	n	OSP	95% CI	n	OSP	95% CI
Overall	**425**	**0.95**	**0.91-0.97**	**411**	**0.82**	**0.78-0.86**	**179**	**0.94**	**0.86-0.98**
< 1				20	0.34	0.14-0.56			
1–4	212	0.96	0.91-0.98	124	0.87	0.79-0.92	96	0.95	0.84-0.98
5–9	213	0.93	0.88-0.97	142	0.87	0.79-0.91	83	0.93	0.74-0.99
10–14				125	0.79	0.68-0.86			

Risk group was unknown for 5 patients.
OSP = overall survival proportion; CI = confidence interval

Exhibit 6.7

Survival outcomes for ALL according to prognostic risk group were available for 836 children aged 0–14 years between 1995 and 2004. The classification of standard risk vs. high risk groups within pediatric ALL was based on the prognostic criteria used at the start of treatment and therapeutic protocol. The interpretation of the data has to take into account that the basis of this prognostic classification has expanded from age, presenting white blood cell count, immunophenotype and CNS involvement to increasingly refined cytogenetic characterization of the blasts and evaluation of early treatment responses (see Introduction).

In the entire cohort of children with ALL included in this analysis, the standard risk and high risk groups each made up half of the cohort (infant ALL in this analysis was classified as high risk). In fact, the high risk group accounted for the majority of ALL patients during 1995–1999 (57.4%) before decreasing to 40.9% during 2000–2004. This distribution of ALL risk groups differs from trial-based data, which show that approximately 25% of all children with B-precursor ALL enrolled in clinical trials are classified as having high risk ALL.[26] It is likely that the introduction of risk classification based on early treatment response (MRD; see Introduction) will affect the distribution of ALL risk groups in subsequent treatment periods.

Treatment approaches were heterogeneous and included study protocols of 2 groups (Children's Oncology Group or predecessors and Dana-Farber Cancer Institute Consortium) as well as treatment protocols adopted by individual centres as standards of care.

				2000–2004					
	High			Standard			High		
	n	OSP	95% CI	n	OSP	95% CI	n	OSP	95% CI
	241	**0.81**	**0.73-0.87**	**246**	**0.95**	**0.91-0.97**	**170**	**0.83**	**0.78-0.88**
	11	0.42	0.14-0.69				9	0.35	0.10-0.61
	79	0.84	0.72-0.91	116	0.96	0.91-0.99	45	0.90	0.79-0.96
	97	0.86	0.72-0.94	130	0.93	0.87-0.96	45	0.85	0.74-0.91
	54	0.76	0.56-0.88				71	0.81	0.70-0.89

The proportion of overall survival after 5 years was 0.95 for children with standard risk ALL and 0.82 for high risk ALL during the entire reporting period (1995–2004). Survival proportions in the age groups 1–4/5–9 years were higher in the standard risk group (0.96/0.93) and lower for high risk patients (0.87/0.87) than in the entire group of children with ALL between the ages of 1 and 9 years (0.91/0.90) (see also Exhibit 6.2). These results are expected because the latter group contains both patients with standard risk and high risk ALL.

In the more recent period (2000–2004), overall survival for standard risk ALL was significantly higher than for all children with high risk ALL (including infant ALL) or children with high risk ALL older than 10 years, suggesting that further improvements in therapeutic efficacy, particularly in the high risk group, remain to be achieved.

Summary

Incidence

ALL was the most common form of childhood leukemia (80.4%), followed by AML (15.6%). ASIRs were 44.4 cases for any form of childhood leukemia, 36.0 for ALL and 7.3 for AML per 1 million population per year. The incidence of leukemia was higher among males (56.0% of ALL, 52.8% of AML).

Mortality

The ASMRs were 10.7 deaths due to any form of childhood leukemia, 6.4 due to ALL and 3.6 due to AML per 1 million population per year. Males with ALL had a higher mortality rate than females; there was no difference for AML. Mortality rates decreased for all leukemias over time, particularly during the most recent reporting period (2000–2004). Mortality, expressed as the number of deaths per number of cases diagnosed, improved particularly for childhood AML (from 59.3% in 1990–1994 to 29.4% in 2000–2004), likely reflecting intensified chemotherapy and supportive care.

Event free and overall survival

EFS and overall survival were 0.71 and 0.81 for all children with leukemia. As expected, EFS and overall survival were higher for children with ALL (0.77 and 0.87, respectively) than for those with AML (0.50 and 0.59, respectively). EFS was lowest in infants (younger than 1 year of age) with ALL (0.37), intermediate for children aged 10 years or older (0.79) and highest in the age group 1–9 years (0.90). The proportion of survival after 5 years was 0.95 for children with standard risk ALL and 0.82 for high risk ALL during the entire reporting period (1995–2004).

Hematopoietic stem cell transplantation

HSCT was part of treatment for 18.7% of children with leukemia (45.8% of those with AML and 11.2% of those with ALL). Most recipients received allografts (97.4% between 2000 and 2004). Most transplants for AML were carried out in first remission. In contrast, transplantation for ALL was most commonly used in second remission. The probability of survival after allogeneic HSCT for all pediatric leukemias was 0.64, for ALL it was 0.66 and for AML, 0.68. The proportion of patients treated for leukemia with HSCT decreased over time as a result of a lower proportion of all children with AML undergoing HSCT.

Relapse

Among children with leukemia, 20.0% developed a relapse (17.8% of those with ALL and 36.9% of those with AML). Relapse occurred more often in males than females. The proportion of children who relapsed decreased over time (by 24.6% for ALL and 30.0% for AML). Most relapses occurred late (more than 36 months from initial diagnosis) in ALL (41.3%) but early (within 18 months of diagnosis) in AML (71.0%). The proportion of children who survived at least 5 years after a relapse was significantly higher for ALL (0.58) than for AML (0.27).

References

1 Group USCSW. United States cancer statistics. 1999–2008 incidence and mortality web-based report, 2012. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Available at http://www.cdc.gov/uscs.

2 Pui C-H, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, et al. Treatment of childhood acute lymphoblastic leukemia without prophylactic cranial irradiation. N Engl J Med. 2009;360:2730-41.

3 Ries LA, Wingo PA, Miller DS, Howe HL, Weir HK, Rosenberg HM, et al. The annual report to the nation on the status of cancer, 1973-1997, with a special section on colorectal cancer. Cancer. 2000;88:2398-424.

4 Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet. 2000;355:165-9.

5 Creutzig U, Zimmermann M, Lehrnbecher T, Graf N, Hermann J, Niemeyer CM, et al. Less toxicity by optimizing chemotherapy, but not by addition of granulocyte colony-stimulating factor in children and adolescents with acute myeloid leukemia: results of AML-BFM 98. J Clin Oncol. 2006;24:4499-506.

6 Gibson BE, Wheatley K, Hann IM, Stevens RF, Webb D, Hills RK, et al. Treatment strategy and long-term results in paediatric patients treated in consecutive UK AML trials. Leukemia. 2005;19:2130-8.

7 Rubnitz JE, Raimondi SC, Tong X, Srivastava DK, Razzouk BI, Shurtleff SA, et al. Favorable impact of the t(9;11) in childhood acute myeloid leukemia. J Clin Oncol. 2002;20:2302-9.

8 Andolina JR, Neudorf SM, Corey SJ. How I treat childhood CML. Blood. 2012;119:1821-30.

9 Pulsipher MA. Treatment of CML in pediatric patients: should imatinib mesylate (STI-571, Gleevec) or allogeneic hematopoietic cell transplant be front-line therapy? Pediatr Blood Cancer. 2004;43:523-33.

10 Loh ML. Recent advances in the pathogenesis and treatment of juvenile myelomonocytic leukaemia. Br J Haematol. 2001;152:677-87.

11 Niemeyer CM, Kratz CP. Paediatric myelodysplastic syndromes and juvenile myelomonocytic leukaemia: molecular classification and treatment options. Br J Haematol. 2008;140:610-24.

12 Locatelli F, Nollke P, Zecca M, Korthof E, Lanino E, Peters C, et al. Hematopoietic stem cell transplantation (HSCT) in children with juvenile myelomonocytic leukemia (JMML): results of the EWOG-MDS/EBMT trial. Blood. 2005;105:410-9.

13 Manabe A, Okamura J, Yumura-Yagi K, Akiyama Y, Sako M, Uchiyama H, et al. Allogeneic hematopoietic stem cell transplantation for 27 children with juvenile myelomonocytic leukemia diagnosed based on the criteria of the International JMML Working Group. Leukemia. 2002;16:645-9.

14 Mullighan CG, Goorha S, Radtke I, Miller CB, Coustan-Smith E, Dalton JD, et al. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature. 2007;446:758-64.

15 Mardis ER, Ding L, Dooling DJ, Larson DE, McLellan MD, Chen K, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. N Engl J Med. 2009;361(11):1058-66.

16 Welch JS, Ley TJ, Link DC, Miller CA, Larson DE, Koboldt DC, et al. The origin and evolution of mutations in acute myeloid leukemia. Cell. 2012;150:264-78.

17 Speck NA, Gilliland DG. Core-binding factors in haematopoiesis and leukaemia. Nat Rev Cancer. 2002;2:502-13.

18 Greaves MF, Maia AT, Wiemels JL, Ford AM. Leukemia in twins: lessons in natural history. Blood. 2003;102:2321-33.

19 Greaves MF, Wiemel J. Origins of chromosome translocations in childhood leukaemia. Nat Rev Cancer. 2003;3:639-49.

20 Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. Nat Rev Cancer. 2006;6:193-203.

21 Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. N Engl J Med. 2004;350:1535-48.

22 Burnett A, Wetzler M, Löwenberg B. Therapeutic advances in acute myeloid leukemia. J Clin Oncol. 2001;29:487-94.

23 Dick JE. Stem cell concepts renew cancer research. Blood. 2008;112:4793-807.

24 Wang JC, Dick JE. Cancer stem cells: lessons from leukemia. Trends Cell Biol. 2005;15:494-501.

25 Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med. 1997;3:730-7.

26 Schrappe M, Stanulla M. Treatment of childhood acute lymphoblastic leukemia. In Pui C-H, editor. Treatment of acute leukemias. Totowa (NJ): Humana Press; 2003, pp. 87-104.

27 Cave H, van der Werff ten Bosch J, Suciu S, Guidal C, Waterkeyn C, Otten J, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia. European Organization for Research and Treatment of Cancer—Childhood Leukemia Cooperative Group. N Engl J Med. 1998;339:591-8.

28 Einsiedel HG, von Stackelberg A, Hartmann R, Fengler R, Schrappe M, Janka-Schaub G, et al. Long-term outcome in children with relapsed ALL by risk-stratified salvage therapy: results of trial acute lymphoblastic leukemia—relapse study of the Berlin-Frankfurt-Munster Group 87. J Clin Oncol. 2005;23:7942-50.

29 Gaynon PS. Childhood acute lymphoblastic leukaemia and relapse. Br J Haematol. 2005;131:579-87.

30 Ko RH, Ji L, Barnette P, Bostrom B, Hutchinson R, Raetz E, et al. Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a therapeutic advances in childhood leukemia consortium study. J Clin Oncol. 2010;28:648-54.

31 Tallen G, Ratei R, Mann G, Kaspers G, Niggli F, Karachunsky A, et al. Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug chemotherapy: results of trial ALL-REZ BFM 90. J Clin Oncol. 2010;28:2339-47.

32 Pui CH, Cheng C, Leung W, Rai SN, Rivera GK, Sandlund JT, et al. Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia. N Engl J Med. 2003;349:640-9.

33 Dini G, Zecca M, Balduzzi A, Messina C, Masetti R, Fagioli F, et al. No difference in outcome between children and adolescents transplanted for acute lymphoblastic leukemia in second remission. Blood. 2011;118:6683-90.

34 Shaw PJ, Kan F, Woo Ahn K, Spellman SR, Aljurf M, Ayas M, et al. Outcomes of pediatric bone marrow transplantation for leukemia and myelodysplasia using matched sibling, mismatched related, or matched unrelated donors. Blood. 2010;116:4007-15.

35 Lipshultz SE. Exposure to anthracyclines during childhood causes cardiac injury. Semin Oncol. 2006;33:S8-14.

36 Pui CH. Toward optimal central nervous system-directed treatment in childhood acute lymphoblastic leukemia. J Clin Oncol. 2003;21:179-81.

37 Lange B. The management of neoplastic disorders of haematopoiesis in children with Down's syndrome. Br J Haematol. 2000;110:512-24.

38 Sorrell AD, Alonzo TA, Hilden JM, Gerbing RB, Loew TW, Hathaway L, et al. Favorable survival maintained in children who have myeloid leukemia associated with Down syndrome using reduced-dose chemotherapy on Children's Oncology Group trial A2971: a report from the Children's Oncology Group. Cancer. 2012;118(19):4806-14.

39 Lo-Coco F, Avvisati G, Vignetti M, Breccia M, Gallo E, Rambaldi A, et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. Blood. 2010; 116:3171-9.

40 Gamis AS. Acute myeloid leukemia and Down syndrome evolution of modern therapy—state of the art review. Pediatr Blood Cancer. 2005;44:13-20.

41 Borowitz MJ, Devidas M, Hunger SP, Bowman WP, Carroll AJ, Carroll WL, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood. 2008;111:5477-85.

42 Creutzig U, Zimmermann M, Ritter J, Reinhardt D, Hermann J, Henze G, et al. Treatment strategies and long-term results in paediatric patients treated in four consecutive AML-BFM trials. Leukemia. 2005;19:2030-42.

43 Smith M, Arthur D, Camitta B, Carroll AJ, Crist W, Gaynon P, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. J Clin Oncol. 1996;14:18-24.

44 Koike K, Matsuda K. Recent advances in the pathogenesis and management of juvenile myelomonocytic leukaemia. Br J Haematol. 2008;141:567-75.

45 Champagne MA, Capdeville R, Krailo M, Qu W, Peng B, Rosamilia M, et al. Imatinib mesylate (STI571) for treatment of children with Philadelphia chromosome-positive leukemia: results from a Children's Oncology Group phase 1 study. Blood. 2004;104:2655-60.

46 Nguyen K, Devidas M, Cheng SC, La M, Raetz EA, Carroll WL, et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. Leukemia. 2008;22:2142-50.

47 Sander A, Zimmermann M, Dworzak M, Fleischhack G, von Neuhoff C, Reinhardt D, et al. Consequent and intensified relapse therapy improved survival in pediatric AML: results of relapse treatment in 379 patients of three consecutive AML-BFM trials. Leukemia. 2010;24:1422-8.

48 Webb DK. Management of relapsed acute myeloid leukaemia. Br J Haematol. 1999;106:851-9.

Published by the Pediatric Oncology Group of Ontario (POGO)

Pediatric Oncology Group of Ontario
480 University Avenue, Suite 1014
Toronto, Ontario M5G 1V2
info@pogo.ca

Canadian cataloging in publication data:

Atlas of Childhood Cancer in Ontario
Includes bibliographical references.
ISBN: (Print) **978-0-9939255-0-4**
ISBN: (Online) **978-0-9939255-1-1**

How to cite this publication:

The production of *Atlas of Childhood Cancer in Ontario* was a collaborative venture. Accordingly, to give credit to individual authors, please cite individual chapters and title, in addition to editors and book title.

For example: Pole JD, Greenberg ML, Sung L, Agha M, Riehl, M. Survival. In: Greenberg ML, Barnett H, Williams J, editors. Atlas of Childhood Cancer in Ontario. Toronto: Pediatric Oncology Group of Ontario; 2015.

This document is available at www.pogo.ca and www.ices.on.ca