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Late effects in survivors of infant leukemia

W Leung[1,2,3], M Hudson[1,2,3], Y Zhu[4], GK Rivera[2,3], RC Ribeiro[2,3], JT Sandlund[2,3], LC Bowman[2,3], WE Evans[3,5], L Kun[4,5] and C-H Pui[2,3]

[1]*After Completion of Therapy Program, Departments of* [2]*Hematology-Oncology,* [4]*Radiation Oncology, and* [5]*Pharmaceutical Sciences, St Jude Children's Research Hospital, Memphis; and* [3]*University of Tennessee, College of Medicine, Memphis, TN, USA*

Little is known about the incidence of and risk factor for late effects of infant leukemia. We evaluated 19 children with acute lymphoblastic leukemia and 15 with acute myeloid leukemia who were diagnosed at age 12 months or younger and have survived for more than 5 years after the diagnosis (median length of follow-up, 13 years; range, 5.7–29 years). Ten patients received chemotherapy alone (group A), 17 received chemotherapy and CNS-directed radiation therapy (CRT) (group B), and seven received chemotherapy, CRT and bone marrow transplantation (group C). The most frequently observed late sequelae included problems in growth (66% of survivors), learning (50%), hypothyroidism (15%), and pubertal development (12%). Cataract, cardiac and hearing abnormalities occurred in 6% of patients. Only eight patients (24%) survive without late effects. In comparison to patients in group A, patients in groups B and C had a higher incidence of having at least one late complication ($P = 0.009$), a greater decrease in height Z score at 5 years after diagnosis ($P = 0.023$), and a higher incidence of academic difficulties ($P = 0.004$). The estimated odds of academic difficulties increased by 18% ($P = 0.032$) for each month younger in age at the time of CRT. These results indicate that late sequelae are common in long-term survivors of infant leukemia and are often related to CRT and the patient's age at the time of CRT. *Leukemia* (2000) **14,** 1185–1190.

Keywords: late effects; infant leukemia; infant ALL, infant AML

Introduction

Much is known about the incidence of and risk factors for the late effects of treatment of acute leukemia in older children.[1] However, very little information exists about this aspect of treatment in infants,[2,3] largely because very few patients have lived long enough for the problem to be assessed.[4–8] The risk of late effects in infants may be very different from that in older children because in infants growth of all organ systems is more rapid, disposition of antineoplastic agents is more variable,[9] and central nervous system (CNS) leukemia is more frequent requiring CNS-directed therapy.[2,8,10] Earlier studies describing small cohorts of infants with brief follow-up periods have not permitted accurate assessment of the risk of each of the many developmentally dependent late effects. As the number of survivors increases, evaluating the risk factors of late morbidity is becoming possible, and increasingly important. This information will not only have an important bearing on the design of future therapeutic regimens but will also identify areas for late effect surveillance and intervention.

We report the treatment sequelae of 34 children diagnosed with acute leukemia at age 12 months or younger, who survived >5 years and have been extensively followed for a median of 13 years. Comprehensive assessment of this relatively large number of long-term survivors allowed us to evaluate the effect of CNS-directed radiation therapy (CRT) and age at the time of CRT on the risk of late effects.

Correspondence: W Leung, St Jude Children's Research Hospital, 332 N Lauderdale Street, Memphis, TN 38105, USA; Fax: (901) 521-9005
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Patients and methods

Patient characteristics

Between May 1970 and July 1994, 38 infants (12 months of age or younger) with newly diagnosed acute myeloid leukemia (AML) and 45 infants with acute lymphoblastic leukemia (ALL) were treated at St Jude Children's Research Hospital. Fifteen infants (39%) with AML and 19 (42%) of those with ALL survived for more than 5 years after the diagnosis. Twenty-three of these 34 survivors have been monitored for more than 10 years after diagnosis. Their characteristics and primary treatment are shown in Table 1. Details of the institutional protocols have been described previously: Total Therapy Studies VII,[11] VIII,[12] IX,[13] X,[14] XI,[15] XII,[16] XIIIA,[17] R11,[18] R15,[19] AML-76,[20] AML-80,[21] ANLL-83,[22] AML87[23] and AML-91.[23] Ten patients received chemotherapy alone (group A), 17 received chemotherapy and CRT (group B), and seven received chemotherapy, bone marrow transplantation (BMT) and CRT (group C). The median age at diagnosis for patients in groups A, B and C was 0.7 (range, 0.2–1), 0.6 (range, 0.2–0.9), and 0.7 (range, 0.3–1) year, respectively ($P = 0.72$). CRT in group C was given as cranial irradiation ($n = 2$), as cranio-

Table 1 Patient characteristics

	AML	*ALL*
Total number	15	19
Sex (M/F)	3/12	12/7
Age at diagnosis (months)		
Median (range)	8 (2–12)	8 (2–12)
≤6 months	6	3
Current age (years)		
Median age (range)	16.3 (6.5–22.3)	12.8 (7.4–29.2)
>10 years from diagnosis	11	12
Primary regimen		
AML 76/80/83/87/91	4/4/2/2/3	—
Total VII/VIII/X/XI/XII/XIIIA	—	1/1/2/8/4/3
Radiation (Gy to cranium)		
None	7	3
Cranial (<10/10–19/≥20)	1/1/5	0/5/3
Craniospinal (10–19/≥20)	0/0	1/4
TBI (10–19)	1	3
BMT		
Autologous/Allogeneic	3/1	0/4
CNS leukemia at diagnosis/relapse	7/2	7/5
Treatment of BM relapse		
R11/R15	—	2/2

TBI, total body irradiation; BMT, bone marrow transplantation; CNS, central nervous system; BM, bone marrow; R11, relapse protocol 11;[18] R15, relapse protocol 15.[19]

spinal irradiation ($n = 1$), or with total body irradiation (TBI) ($n = 4$). The median age at CRT for patients in groups B and C was 1.8 year (range, 0.3–3.1) and 1.4 year (range, 0.7–1.8), respectively. One of the patients in group A received busulfan and cyclophosphamide but no radiation before autologous BMT.

Routine follow-up procedures

After completing therapy all patients received comprehensive assessment at least annually by a primary attending oncologist or, after 1984, in our After Completion of Therapy Clinic to monitor remission status and late effects of treatment. A four-page questionnaire was completed annually in the clinic eliciting information on current medical status, social history and academic progress, among others. Urine analysis, blood cell counts, serum electrolytes and liver function tests were routinely evaluated in all patients. Thyroid function tests were routinely performed in patients who had received CRT. Electrocardiogram and echocardiogram were routinely evaluated at least every 2 to 3 yearly in patients who had received anthracyclines or BMT. Pulmonary function tests were also routinely performed at least every 2 to 3 yearly in all BMT patients. Other laboratory tests were performed based on the findings of the questionnaires and clinical grounds.

Patients 18 years or older are discharged from the institution and followed thereafter by their local physicians. The status of these patients is monitored by a two-page questionnaire mailed annually by the hospital's tumor registry, eliciting information regarding current medical status, history of hospitalization, medications and schooling, among others. Reports of serious sequelae are confirmed by contacting the local physicians and the survivor or his or her family, and reviewing medical records and pathology reports from local hospitals. At the time of this report, 29 (85%) patients had follow-up within the last year, 32 (94%) patients within the last 2 years, and all patients within the last 3 years. The median length of follow-up was 13 years (range 5.7–29 years).

Late complications

Late complications were determined by review of computer database and medical record and were categorized as follows. *Cardiovascular*: abnormalities detected by clinical cardiovascular examination, diagnostic imaging (echocardiograms or chest radiograph), or electrocardiogram. *Endocrine*: clinical evidence of endocrine dysfunction (eg delayed pubertal development,[24,25] abnormal menstrual patterns), abnormalities of serum thyroid, gonadotropin, androgen or estrogen levels, or use of hormonal replacement therapy. *Growth*: fall in height Z score by >2 standard deviation (s.d.), fall in weight Z score by >2 s.d., or gain in weight Z score by >2 s.d. at follow-up since diagnosis; or abnormalities of serum insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), or growth hormone by provocative testing. Weight Z scores were calculated similar to that of height Z scores: (height minus mean height for sex and age) divided by s.d. of height for sex and age.[26] *Neurocognitive*: clinical neurological disorders (eg seizure, hearing loss, speech delay); abnormal diagnostic imaging, electroencephalogram, or audiometric testing; abnormal neuropsychologic evaluation of global intellect and academic achievement (Wechsler Intelligence Scales and Wide Range Achievement Test).[27,28] *Ophthalmologic*: abnormalities detected by clinical ophthalmologic examination. *Pulmonary*: clinical symptoms suggesting pulmonary dysfunction (eg exertional dyspnea), abnormalities of spirometry or diffusing capacity by pulmonary function testing.

Statistical analysis

The Wilcoxon rank sum test or Kruskal–Wallis test was used to compare the height or weight changes since diagnosis between two treatment groups or among all three treatment groups, respectively.[29] Differences in the incidences (odds) of late effects by different risk categories were compared by exact tests.[30] The relationship of late effects to the patient's age at the time of CRT or to the dose of CRT (both as continuous variable) were examined by exact logistic regression analysis.[31] Due to the small sample size in each subgroup of patients, multivariate analysis was not attempted.

Results

At least one late complication was observed in 26 of the 34 (76%) patients. Six patients in group A (60%), two patients in group B (12%), and none in group C (0%) had no observed late effects thus far ($P = 0.009$), with a median follow-up of 12.2, 16.9, and 8.0 years, respectively.

Growth

Changes in height and weight Z scores at 5 years, 10 years or 15 years after diagnosis were analyzed. The height and weight Z scores were stable (changed less than 2 s.d. since diagnosis) in 15 patients (44%) at all of the time-points evaluated.

In comparison to patients in group A, patients in group B had a greater decrease in height Z scores, whereas patients in group C had the greatest decrease in height Z scores since diagnosis (Figure 1, $P = 0.023$ by Kruskal–Wallis test at 5 years). No patient in group A had height Z score falling >2 s.d. since diagnosis (Table 2). The height Z score decreased by >2 s.d. at last follow-up in three patients (18%) in group B and five patients (71%) in group C. The decrease in height Z scores was greatest in patients who received craniospinal radiation or TBI (Figure 2). Six patients (three each from

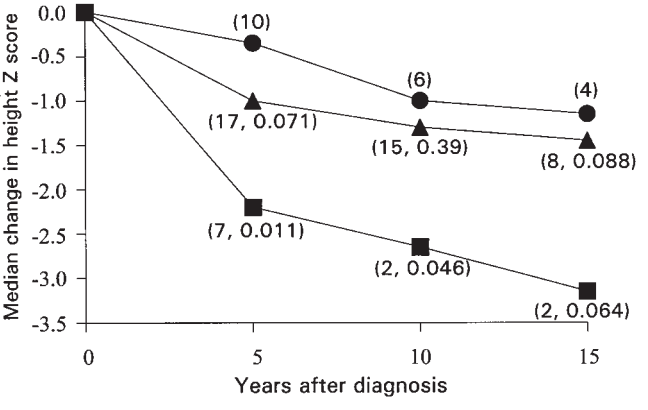

Figure 1 Median change in height Z scores since diagnosis. The number of patients evaluated (n) and the P value by Wilcoxon rank sum test comparing patients in group A (●) with patients in group B (▲) or group C (■) are shown (n, P).

Table 2 Growth after diagnosis

	Group A (CT only)	*Group B (CT + CRT)*	*Group C (CT + CRT + BMT)*
Five years since diagnosis	*n* = 10	*n* = 17	*n* = 7
Decrease in height Z score >1 s.d., >2 s.d.	20%, 0%	41%, 12%	71%, 57%
Decrease in weight Z score >1 s.d., >2 s.d.	10%, 0%	18%, 18%	43%, 14%
Increase in weight Z score >1 s.d., >2 s.d.	20%, 10%	24%, 12%	14%, 0%
Ten years since diagnosis	*n* = 6	*n* = 16 (15)[a]	*n* = 2
Decrease in height Z score >1 s.d., >2 s.d.	50%, 0%	60%, 20%	100%, 100%
Decrease in weight Z score >1 s.d., >2 s.d.	33%, 0%	25%, 6%	100%, 100%
Increase in weight Z score >1 s.d., >2 s.d.	33%, 0%	44%, 25%	0%, 0%
Fifteen years since diagnosis	*n* = 4	*n* = 9 (8)[a]	*n* = 2
Decrease in height Z score >1 s.d., >2 s.d.	50%, 0%	88%, 13%	100%, 100%
Decrease in weight Z score >1 s.d., >2 s.d.	25%, 0%	22%, 11%	100%, 100%
Increase in weight Z score >1 s.d., >2 s.d.	25%, 0%	33%, 0%	0%, 0%

[a]One of the patients received growth hormone treatment and was not analyzed for height.
CT, chemotherapy; CRT, CNS-directed radiation therapy; BMT, bone marrow transplantation; *n*, number of patient evaluated (censored at last follow-up).

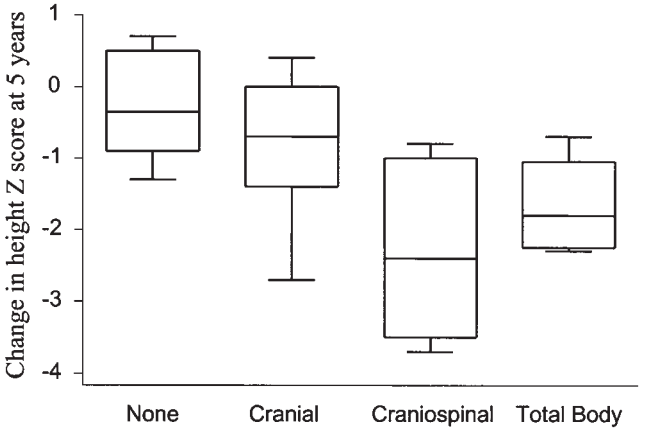

Figure 2 Box plots by radiation group the changes in height Z scores at 5 years after diagnosis. The line in the middle of the box represents the 50th percentile and the box extends from the 25th to the 75th percentile. The lines emerging from the box extend to the largest or the lowest data point. $P = 0.0126$ by Kruskal–Wallis test.

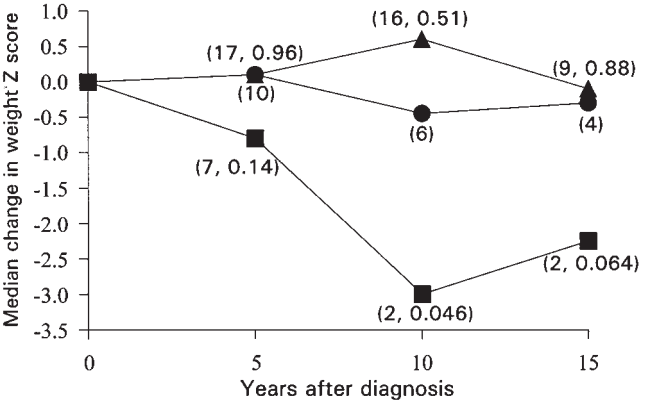

Figure 3 Median change in weight Z scores since diagnosis. The number of patients evaluated (*n*) and the *P* value by Wilcoxon rank sum test comparing patients in group A (●) with patients in group B (▲) or group C (■) are shown (*n*, *P*).

groups B and C) had growth hormone deficiency confirmed by blood testing. Of these, two declined and four received growth hormone replacement therapy.

Except one patient with an increase in weight Z score >2 s.d. at 5 years, the weight Z scores of patients in group A had not changed significantly since diagnosis (Table 2, Figure 3). In contrast, the weight Z scores of patients in group C decreased after diagnosis (Figure 3). The change in weight Z scores was heterogeneous in group B: at each time-point analyzed, approximately half of the patients had an increase in weight Z score while another half had a decrease in weight Z score. The weight Z scores of patients in group B decreased by >2 s.d. since diagnosis in three patients (all boys) but increased by >2 s.d. since diagnosis in four patients (two boys and two girls) on at least one of the time-points analyzed (Table 2).

Other endocrine function

Hypothyroidism requiring replacement therapy was found in five (21%) of the 24 patients (three from group B and two from group C) 4–13 years after CRT was completed. Serum thyroid function tests were normal in 17 patients and were not performed in two patients. All these 19 patients were clinically euthyroid.

Ten patients were appropriately prepubertal at the time of this study. For the other 24 patients, 20 entered and progressed through puberty normally, reaching Tanner stages of puberty at the appropriate age. Three (two from group B and one from group C) had precocious puberty with menarche at the age of 8 to 9.8 years. One patient from group B had delayed puberty and hypogonadism after testicular irradiation for bilateral testicular relapse.

Neurocognitive function

Review of the annual questionnaires and psychology reports showed that 17 patients (50%) did not have any academic problems. The other 17 patients had academic difficulties requiring special tutoring or placement in special education classes. Six of these children (four in group B and two in group C) had a seizure disorder and moderate to severe neurocognitive deficits with a median full-scale intelligence estimate (IQ)

of 35 (range 7–68). Six patients had a full-scale IQ estimate ranged from 60 to 84. Three patients had an IQ estimate in the normal range: one with attention deficit disorder and another with low verbal processing speed. Two patients were identified as having learning disability by the local school personnel but were not formally tested at SJCRH.

In comparison to patients in group A, patients in groups B and C had higher incidences of academic difficulties (10%, 59% and 86%, respectively, $P = 0.004$). Younger age at the time of CRT was associated with an increased risk of learning problems. The estimated odds of academic difficulties increased by 18% (95% CI 0.17–61%, $P = 0.032$) for each month younger in age at the time of CRT (Figure 4). With three quarters of patients receiving a narrow range of doses of CRT (18–24 Gy), no association was found in this study between the dose of CRT and the development of academic difficulties ($P = 0.77$).

Cardiopulmonary functions

Serial electrocardiogram and echocardiogram were all normal in 13 of the 15 AML patients and in all of the 12 ALL patients tested. One patient in group C had thickening of the left ventricular wall but normal contractility (shortening fractions 36–39%) that was found 13 years after receiving TBI (12 Gy), cyclophosphamide (2.2 g/m^2) and anthracyclines (200 mg/m^2). Another patient in group A had mild left ventricular dilatation and cardiomyopathy (shortening fraction 24–30%) that developed 9 years after receiving cyclophosphamide (3.2 g/m^2) and anthracyclines (350 mg/m^2). Spirometry, lung volumes and diffusing capacity were all within normal limits (>80% predicted) on serial testings in the eight patients who had received BMT.

Other late sequelae

Two of the seven patients in group C had cataracts that were diagnosed 9–11 years after the completion of TBI, whereas all ophthalmologic examinations were normal in groups A and B ($P = 0.037$). Two of 34 patients (one each from groups A and C) had speech delay and hearing loss requiring a hearing aid.

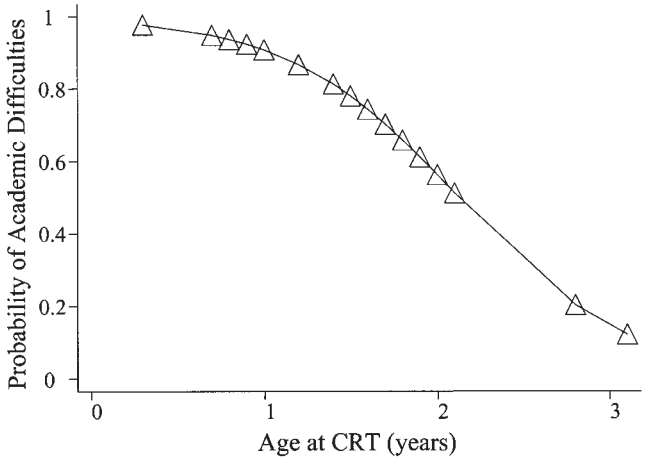

Figure 4 Fitted logistic dose–response relationship. Predicted probability of academic difficulties as a function of age at which CRT was administered.

Papillary thyroid carcinoma developed in one patient 25 years after craniospinal irradiation (total dose 24 Gy); this patient is free of disease 3 years after surgery.

Discussion

We describe the incidence and severity of treatment sequelae in a cohort of long-term survivors of infant leukemia treated with contemporary therapy. Our results indicate that late morbidity is very common, with three-quarters of our cohort exhibiting abnormalities affecting growth, endocrine, neurocognitive, cardiac, ophthalmologic and/or audiologic function. Many of these late effects can be directly attributed to CRT and the young age at the time of CRT.

Growth problems, as manifested by changes in height or weight Z scores >2 s.d. since diagnosis, represented one of the most common late sequelae in this cohort. In general, patients who received chemotherapy alone had normal growth, whereas patients who received additional CRT and BMT (group C) had poor height and weight gain. Patients who received CRT but not BMT (group B) had a slight height compromise that may or may not be accompanied by parallel weight compromise. The growth pattern was least predictable in this latter group of survivors: while some had poor weight gain, others developed obesity. The biological reason for this heterogeneity in weight gain after CRT is uncertain.[32,33]

This study confirms and extends the prior finding of an association between CRT and neurocognitive deficits observed in smaller patient cohorts at our institution and at others.[27,34–36] We show for the first time that the estimated odds of development of academic difficulties increase by 18% for each month younger in age at the time of CRT. Although intensive CNS-directed chemotherapy may also adversely affect the immature CNS,[28,35,37] its impact is likely to be less than that of CRT. Indeed, Kaleita *et al*[38] recently showed a substantial improvement in neurodevelopmental outcomes of infant leukemia survivors evaluated at a mean age of 5 years who were treated on the CCG107 protocol that does not include CRT. In our study, only one of the 10 patients (in group A) who did not receive CRT has academic difficulties. These 10 patients have been in school for a median of 7.5 years (range, 2.5–17 years), which should allow sufficient time for the identification of significant neurocognitive deficits. Taken together, these results support the contemporary trend of avoiding CRT in young children, even those with CNS leukemia at the time of diagnosis.[6,7] For young children who require CRT, our age-effect data emphasize the potential benefit of delaying CRT until the child is older. The probability of having academic difficulties decreased by approximately 50% if CRT administration was delayed until the child was 2 years of age instead of soon after diagnosis (Figure 4).

Our study is not without limitations. First, the retrospective nature of this study predisposes specific limitations. Incomplete surveillance and noncompliance with recommended follow-up may contribute to under or over-estimation of treatment-related toxicity. Propitiously, 29 (85%) of our 34 patients were last evaluated by an oncologist or a primary care physician within 1 year of this analysis. Second, although 23 patients (68%) have survived for more than 10 years after the diagnosis, the length of follow-up may still be short for some late sequelae, as illustrated by the secondary malignancy which was diagnosed 25 years after therapy in one of our patients. Brief follow-up may create bias in the comparison of patients who received CRT and those who did not, because

late effects in patients who were not treated with CRT may remain latent for a longer period of time. Continuous, long-term follow-up of this cohort and others will be necessary to evaluate this possibility.

In summary, the incidence and risk factor for a wide spectrum of late sequelae has been described in this study of long-term survivors of infant leukemia. These findings should provide valuable information for individual risk assessment and for defining areas of surveillance and intervention. Early identification and treatment of late sequelae should improve the quality of life for many long-term survivors.

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