PERGAMON

European Journal of Cancer 39 (2003) 359–365

European Journal of Cancer

www.ejconline.com

Intellectual outcome in children and adolescents with acute lymphoblastic leukaemia treated with chemotherapy alone: age- and sex-related differences

N. von der Weid*, I. Mosimann, A. Hirt, P. Wacker, M. Nenadov Beck, P. Imbach, U. Caflisch, F. Niggli, A. Feldges, H.P. Wagner

Swiss Pediatric Oncology Group (SPOG), University Children's Hospital Inselspital, CH-3010 Berne, Switzerland

Received 18 September 2001; received in revised form 25 April 2002; accepted 17 June 2002

Abstract

One of the most relevant concerns in long-term survivors of paediatric acute lymphoblastic leukaemia (ALL) is the development of neuropsychological sequelae. The majority of the published studies report on patients treated with chemotherapy and prophylactic central nervous system (CNS) irradiation, little is known about the outcome of patients treated with chemotherapy-only regimens. Using the standardised clinical and neuropsychological instruments of the SPOG Late Effects Study, the intellectual performance of 132 paediatric ALL patients treated with chemotherapy only was compared to that of 100 control patients surviving from diverse non-CNS solid tumours. As a group, ALL and solid tumour survivors showed normal and comparable intellectual performances (mean global IQ 104.6 in both groups). The percentage of patients in the borderline range (global IQ between 70 and 85) was comparable and not higher as expected (10% cases and 13% controls, expected 16%). Only 2 (2%) of the former ALL and 1 (1%) of the solid tumour patients were in the range of mental retardation (global IQ < 70). Former known risk factors described in children treated with prophylactic CNS irradiation, like a younger age at diagnosis of ALL and female gender, remained valid in chemotherapy-only treated patients. The abandonment of prophylactic CNS irradiation and its replacement by a more intensive systemic and intrathecal chemotherapy led to a reduction, but not the disappearance of late neuropsychological sequelae.

Keywords: ALL; Childhood; Age; Gender; Chemotherapy; Late effects; Neuropsychology

1. Introduction

With the use of more intensive regimens systematically, including prophylactic central nervous system (CNS) treatment, the prognosis of children with acute lymphoblastic leukaemia (ALL) has dramatically improved over the last four decades, with the overall survival rate currently reaching 75–80% [1]. During the 1970s and early 1980s, cranial irradiation, with or without intrathecal chemotherapy, was the mainstream of prophylactic CNS therapy. Usual doses ranged between 18 and 24 Gy. Neuropsychological abnormalities following CNS irradiation have been reported in numerous studies [2—9]. As a consequence, new treatment strategies using more intensive systemic and intrathecal chemotherapy regimens without cranial irradiation have been developed and have shown comparable efficacy in preventing CNS disease [10,11]. In the last 10 years, several studies focusing on the neuropsychological outcome of children with ALL treated without prophylactic cranial irradiation have been published [12—21]. Results have been controversial, some reports showing deleterious effects of combined (i.e. intravenous (i.v.) and intrathecal) methotrexate (MTX) [14–18], others having shown no important cognitive deficits [19–21].

The aim of this cross-sectional, nationwide study, was to assess the intellectual outcome of ALL survivors treated with chemotherapy-only regimens and to see whether risk factors for a poorer outcome formerly described in irradiated children, like age at diagnosis and female gender, also represent a risk factor for children treated without CNS irradiation.

* Corresponding author. Tel.: +41-31-632-9495; fax: +41-31-632-9507.

E-mail address: nvdweid@insel.ch (N. von der Weid).

0959-8049/03/$ - see front matter
PII: S0959-8049(02)00260-5

2. Patients and methods

During 1994–1996, 450 survivors of childhood cancer, diagnosed in Switzerland between 1976 and 1989, were assessed for the late effects of treatment using a standardised set of instruments (SPOG Late Effects Study [22]). Briefly, besides patient's history and clinical investigation, the usual laboratory tests (complete blood counts, liver and renal function, urinalysis), a comprehensive endocrinological status and if needed more specific tests (e.g. electrocardiogram (ECG)/echocardiography, lung function, electroencephalogram (EEG)/cranial magnetic resonance imaging (MRI) were done. For each patient, the socio-economic status (SES) of the family was determined by means of a six-point scale for both paternal occupation and maternal education [23]; the lowest score being 2 and signifying the highest SES, the highest score being 12 and signifying the lowest SES.

Intellectual performances were assessed using the Wechsler's Intelligence Test for Children (WISC-R) adapted for different ages and languages [24]. The German versions were the HAWIK-R for Swiss German children (6–15 years of age), revised 1988, and the HAWIE-R for young adults (>15 years), revised 1991. The French adaptations were the French WISC-R and WAIS-R, both revised 1991. The detailed methodology as well as the rules for interpreting the results were those of the test manual; briefly, the mean intelligence quotient (IQ) score in the general population is 100 with a standard deviation (S.D.) of ± 15, the mean value points for the individual items of the test are 10 with a S.D. of ± 2. Patients with a global IQ < 85 are in the borderline range, those with a global IQ < 70 are mentally retarded.

Among the 450 long-term survivors assessed in the SPOG late effects study, 196 were ALL survivors and represented almost 90% of all ALL survivors known from SPOG (data from the SPOG registry, Berne, Switzerland, unpublished). To be eligible, patients had to be alive with no evidence of disease for 5 or more years after diagnosis and to be off-therapy for at least 2 years. 2 patients having undergone bone marrow transplantation, 4 patients with trisomy 21 and 48 children having undergone prophylactic CNS irradiation were excluded. The remaining 142 patients were eligible for the current study. 10 of them were not fluent enough either in German or in French and were therefore excluded. None of the included 132 patients had initial CNS infiltration, or other pre-existing neurological or psychiatric conditions, and all were surviving in first CCR after regimens without cranial irradiation.

Three main treatment protocols have been used, each accruing appoximately one-third of the studied ALL patients: (i) ALinC#13 (Paediatric Oncology Group (POG) 8036) where CNS prophylaxis consisted of 20 triple intrathecal (TIT) injections (MTX, Hydrocortisone and Ara-C, age-dependent doses, maximum 15/15/30 mg/TIT) combined with six doses of i.v. MTX (60 mg/m^2/dose) during consolidation; (ii) ALinC#14 (POG 8602) with 19 TIT (same doses as in #13) combined with 6 i.v. intermediate-dose MTX (IDM) infusions (1 g/m^2/24 h) with leucovorin rescue during consolidation; (iii) SPOG ALL 79/84 (adapted from the LS_2A_2 study) with 25 TIT (same doses as POG) combined with 3 i.v. IDM (0.5 g/m^2/1 h) infusions during consolidation and 5 i.v. IDM (1 g/m^2/1 h) infusions with leucovorin rescue plus five low-dose p.os. MTX courses (10 mg/m2/day×4 days) during maintenance I. Long-term maintenance therapy to an overall treatment duration of 21/2 years consisted in weekly intra-muscular or oral MTX (20 mg/m^2/week) and p.os 6-mercaptopurine (6-MP) (50 mg/m^2/day) for all the three protocols. The glucocorticosteroid drug used during the 4-week induction and later on was prednisone in all the three studies. Patients demographics are summarised in Tables 1 and 2.

Table 1
Demographic data of ALL survivors and controls

	Controls ($n=100$)	ALL patients ($n=132$)
Age at Dx (years) median (range)	5.4 (0.1–15.7)	4.8 (0.6–14.5)
Age at study (years) median (range)	15.8 (6.3–25.0)	14.7 (6.8–33.7)
Gender		
Girls (N)	46	66
Boys (N)	54	66
F:M ratio	1:1.2	1.0:1.0
Mean SES	5.0 (S.D. 1.86)	4.25 (S.D. 2.45)

Dx, diagnosis; SES, socio-economic status; F:M, female:male; ALL, acute lymphoblastic leukaemia.

Table 2
Distribution of age and gender among ALL survivors

	Girls with ALL ($n=66$) median	Boys with ALL ($n=66$) median	ALL ⩽6 yrs ($n=83$) median	ALL >6 yrs ($n=49$) median
Age at Dx (range)	4.5 (1.4–14.5)	5.1 (0.6–14.2)	3.8 (0.6–6.0)	9.3 (6.1–14.5)
Age at study (range)	13.5 (6.8–28.3)	16 (7.5–33.7)	12.5 (6.8–25.5)	18.5 (12.2–33.7)

Besides brain integrity and SES, intellectual performances are dependent on a lot of other factors like psycho-familial background, impact of the cancer experience, school absences, etc. In order to control for these potentially confounding variables, we chose a control group, matched for age at diagnosis and gender (see Table 1), from the population of children with solid tumours assessed in the Late Effects study, during the same time period and with the same instruments. These children and young adults had been treated for Wilms' tumours ($N=31$), liver tumours ($N=2$), non-CNS germ cell tumours ($N=8$), bone tumours ($N=14$), soft-tissue sarcomas outside the head and neck region ($N=25$) and Hodgkin's disease ($N=20$).

2.1. Statistics [25]

The Mann–Whitney U-test was used to check for potential differences in ages, gender and SES between the ALL and control group. Differences in the frequency of borderline or pathological IQs in the studied populations were assessed using contingency tables and the χ^2-test.

In a first step, an univariate analysis was performed to study the impact of age at diagnosis and gender on the IQ scores and single items of the WISC-R test in ALL and in control patients respectively. In a second step, a multivariate linear regression analysis was undertaken, to assess the independent impact of each one of the four relevant variables: age at diagnosis (Dx), age at study (Sx), gender and SES of the family. Standardised beta coefficients as markers of the effect size were determined.

All analyses were performed with the statistical software S-Plus 2000 (Insightful Corp., Seattle, WA, USA). Because multiple comparisons were performed, only P values <0.010 were considered statistically significant throughout.

3. Results

3.1. ALL patients as a group versus controls

Lower socio-economic scales were slightly underrepresented in both ALL patients and controls, but there was no statistically significant difference between the two groups. Globally, ALL patients and controls showed normal and comparable results in terms of global, verbal and performance IQs. The results in the different items of the test were all in the normal range (Table 3).

13 (10%) of the 132 ALL survivors compared with 13 (13%) of the 100 controls were in the borderline range (gIQ between 70 and 85). Theoretically, in an ideally distributed random population, 16% would be expected to be in this range.

Table 3
Global results in the ALL versus control group

	ALL ($n=132$)		Controls ($n=100$)		P value
	Mean	S.D.	Mean	S.D.	
gIQ	104.6	16.2	104.6	16	0.98
pIQ	105.6	16.1	104.2	15.9	0.5
vIQ	102.5	16.1	104.1	15.9	0.46
I	9.6	2.8	9.7	3.2	0.79
C	11	3.2	11	3.1	0.88
Ar	10.3	3	10.5	3	0.63
Si	10.6	2.8	11	2.7	0.35
Vo	9.9	2.8	10.2	2.8	0.47
DS	9.5	2.9	9.8	2.9	0.45
Co	10.4	2.9	10.3	2.8	0.64
PC	11.2	3.1	10.7	3.3	0.2
PA	10.8	2.8	10.9	2.9	0.84
BD	11.1	3.4	11.1	3.3	0.95
OA	11.3	3.2	10.9	2.9	0.35

S.D., standard deviation; IQ, intelligence quoheint.

gIQ, global IQ; pIQ, performance IQ; vIQ, verbal IQ; Verbal tests: I, information; C, comprehension; Ar, arithmetics; Si, similarities; Vo, vocabulary; DS, digit span; Performance tests: Co codes; PC picture completion; PA, picture arrangement; BD, block design; OA, object assembling.

Looking at patients in the range of mental retardation (gIQ <70), only 2 (2%) ALL survivors and 1 (1%) control were found. Noteworthy, the 2 ALL patients were very young at the time of diagnosis (1.9 and 2.7 years old, respectively).

In both groups, the percentage of children and young adults with high global IQ (gIQ >115) was identical (26%) and higher than theoretically expected (16%).

3.2. Differences in intellectual outcomes within the group of ALL survivors: impact of age at diagnosis and gender

3.2.1. Univariate analysis

In order to look at whether the age at diagnosis could play a role in long-term intellectual outcome, ALL survivors were divided into two subgroups: (i) children younger than or equal to 6 years (preschool age) and (ii) children older than 6 years at the time of the diagnosis of ALL. Eighty-three children (38 boys and 45 girls) were in the younger group, 49 (28 boys and 21 girls) in the older group.

In both groups, normal results were found for the 3 IQ scores (Table 4) but the younger group scored steadily 6–9 IQ points lower than the older one. The differences were statistically highly significant for the full-scale (global) and the non-verbal (performance) IQs, borderline for the verbal IQ.

Younger children performed significantly poorer than the older ones in one of the six verbal ('Comprehension': 2 value points lower, $P=0.001$) and in two of the

Table 4
Role of the age at diagnosis in 132 ALL survivors; univariate analysis

	⩽6 years ($n=83$)		>6 years ($n=49$)		P value
	Mean	SD	mean	SD	
gIQ	**101.4**	14.8	**110.1**	17.1	**0.002**
pIQ	**102.2**	14.8	**111.3**	16.7	**0.001**
vIQ	**100.2**	15.1	**106.4**	17.1	**0.03**
I	9.6	2.6	9.6	3.1	0.99
C	**10.3**	2.9	**12.2**	3.3	**0.001**
Ar	10.1	2.9	10.7	3	0.25
Si	**10.1**	2.6	**11.5**	2.9	**0.01**
Vo	9.7	2.8	10.3	2.8	0.24
DS	9.4	2.7	9.8	3	0.36
Co	10.3	2.7	10.6	3.2	0.65
PC	10.9	3	11.7	3.1	0.15
PA	10.6	3.1	11.3	2.1	0.18
BD	**10.2**	3.1	**12.6**	3.4	<**0.001**
OA	**10.4**	2.8	**12.8**	3.2	<**0.001**

gIQ, global IQ; pIQ, performance IQ; vIQ, verbal IQ; Verbal tests: I, information; C, comprehension; Ar, arithmetics; Si, similarities; Vo, vocabulary; DS, digit span; Performance tests: Co codes; PC picture completion; PA, picture arrangement; BD, block design; OA, object assembling.

Table 5
Role of the gender in 132 ALL survivors: univariate analysis

	Girls ($n=66$)		Boys($n=66$)		P value
	Mean	S.D.	Mean	S.D.	
gIQ	**99.7**	16.1	**109.5**	14.8	<**0.001**
pIQ	**101.7**	15.7	**109.4**	15.6	**0.005**
vIQ	**97.8**	16.6	**107.2**	14.2	<**0.001**
I	**8.9**	2.6	**10.3**	2.9	**0.005**
C	**10**	3.1	**12**	3	<**0.001**
Ar	**9.6**	3	**11**	2.7	**0.008**
Si	**9.7**	2.9	**11.5**	2.4	<**0.001**
Vo	**9.3**	2.8	**10.5**	2.8	**0.02**
DS	9.3	3	9.7	2.8	0.47
Co	**11**	3.2	**9.9**	2.4	**0.04**
PC	**10.4**	2.8	**12**	3.1	<**0.001**
PA	**10**	2.8	**11.7**	2.6	<**0.001**
BD	**10.1**	3.2	**12.1**	3.3	<**0.001**
OA	**10.7**	2.8	**11.9**	3.4	**0.03**

gIQ, global IQ; pIQ, performance IQ; vIQ, verbal IQ; Verbal tests: I, information; C, comprehension; Ar, arithmetics; Si, similarities; Vo, vocabulary; DS, digit span; Performance tests: Co codes; PC picture completion; PA, picture arrangement; BD, block design; OA, object assembling.

five non-verbal items ('Block design' and 'Object assembling': 2 value points lower, $P<0.001$). In these two non-verbal items, the percentage of children with scores lower than 8 value points (−1 S.D.) were 2-fold higher (17% versus 8% for 'BD', $X^2=2.0$, non-significant (N.S.) and fourfold higher (17% versus 4% for 'OA', $X^2=4.68$, $P<0.05$) in the younger than in the older age groups.

The same analyses were done in the control group and showed no statistically significant differences between the two age groups (data not shown).

When analysing the data separately for boys and girls (Table 5), the first observation is that each group showed normal IQ scores and results in the single items.

Strikingly, and often statistically highly significant, sex-related differences could be observed in the results, girls scoring almost always significantly poorer than boys. Females scored approximately 10 points lower than males in the 3 IQs; 10 (15%) of the 66 girls versus 3 (5%) of the 66 boys were in the borderline range of performances ($\chi^2=4.18$, $P<0.05$). Only 9 (14%) girls reached a gIQ > 115 compared with 25 (38%) of the boys ($\chi^2=10.14$, $P<0.005$).

Gender-specific differences were found in almost all of the 11 single items of the Wechsler's test. In nine of them, girls scored significantly poorer than boys, with 1.2–2 points disparity. Girls and boys scored equally in 'Digit Span' (short-time auditive memory), girls were slightly better ($P=0.04$) in 'Codes', an item assessing visual attention and speed of processing. The following results were found when looking at the number of patients under 8 value points (−1 S.D.) in the single items: 'Information': 12 girls (G) versus 4 boys (B) ($\chi^2=4.55$, $P<0.05$); 'Similarities': 15 G versus 1 B ($\chi^2=8.3$, $P<0.005$); 'Picture Assembling' : 13 G versus 3 B ($\chi^2=7.11$, $P<0.01$); 'Block Design': 13 G versus 5 B ($\chi^2=4.12$, $P<0.05$).

The same analyses were done in the control group and showed no statistically significant differences between the girls and boys (data not shown).

3.2.2. Multivariate analysis

The results of the linear regression analysis including the four variables of interest (age at diagnosis, age at study, gender and SES) are summarised in Table 6. Age at study and SES had absolutely no effect, either on global intellectual function or on any of the single items. Age at diagnosis, entered as continuous variables, had a clear-cut influence on global IQ ($P=0.009$), a tendency was observed for verbal and non-verbal IQs ($P=0.021$ and $P=0.012$, respectively), younger children scoring lower than older ones. For global IQ, the standardised beta coefficient was 0.31, indicating that an increase of 1.0 S.D. in age at diagnosis produced an increase of 0.31 S.D. in gIQ.

In the multivariate setting, gender was the most powerful single prognostic factor of intellectual performances, clearly influencing the three IQ scores and many single items: Information, Comprehension, Arithmetic's and Similarities in the verbal scale, Picture Completing, Picture Assembling and Block Design in the non-verbal scale. The standardised beta coefficients were computed for male sex and indicated a clear-cut positive impact on the same items. One exception was

Table 6
Multivariate analysis in 132 ALL survivors; independent impacts of age at diagnosis (Dx), gender, age at study (Sx) and SES

	Age at Dx		Gender		Age at Sx		SES	
	β	*P* value	β	*P* value	β	*P* value	β	*P* value
gIQ	0.31	**0.009**	0.29	<**0.001**	−0.09	0.433	0.09	0.258
pIQ	0.30	0.012	0.22	**0.009**	−0.07	0.542	0.12	0.167
vIQ	0.28	0.021	0.29	<**0.001**	−0.15	0.200	0.06	0.510
I	0.13	0.296	0.26	**0.004**	−0.17	0.177	0.03	0.715
C	0.21	0.080	0.29	<**0.001**	0.03	0.796	0.02	0.801
Ar	0.14	0.264	0.23	**0.010**	−0.07	0.577	0.12	0.175
Si	0.25	0.039	0.31	<**0.001**	−0.05	0.682	0.03	0.675
Vo	0.22	0.071	0.21	0.015	−0.14	0.239	0.03	0.670
DS	0.14	0.275	0.06	0.506	−0.07	0.598	0.09	0.317
Co	0.17	0.186	−0.18	0.046	−0.10	0.416	0.05	0.589
PC	0.22	0.067	0.26	**0.004**	−0.12	0.311	0.07	0.396
PA	0.22	0.069	0.31	<**0.001**	−0.22	0.070	0.08	0.333
BD	0.26	0.025	0.28	**0.001**	0.01	0.945	0.10	0.198
OA	0.28	0.017	0.15	0.073	0.13	0.275	0.17	0.037

gIQ, global IQ; pIQ, performance IQ; vIQ, verbal IQ; Verbal tests: I, information; C, comprehension; Ar, arithmetics; Si, similarities; Vo, vocabulary; DS, digit span; Performance tests: Co codes; PC picture completion; PA, picture arrangement; BD, block design; OA, object assembling.

'Codes' with a negative impact of male sex, but not reaching statistical significance ($\beta = -0.18$; $P = 0.046$).

The multivariate analysis with the same four variables of interest was also performed in the group of control patients with solid tumours and showed absolutely no impact, either on the IQ scores, or on any of the single items.

4. Discussion

Our findings support the observations from Jankovic and colleagues [8], Butler and colleagues [20] and Kingma and colleagues [21] that chemotherapy-only regimens lead to fewer and less severe long-term neurotoxicity than former regimens that combined cranial irradiation and chemotherapy. As a group, ALL survivors showed intellectual performances within the normal range and comparable to those of survivors from solid tumours outside the CNS. The percentage of patients in the borderline range of IQ (70–85) or mentally retarded (<70) was similar in both groups and lower than expected.

Age at diagnosis of ALL has been shown to be an essential prognostic factor for the intellectual outcome of children treated with prophylactic cranial irradiation [5,6]. We found that this factor also plays a role, although more modest, in children treated with chemotherapy alone. In the univariate analysis comparing two age groups (6 years and under and more than 6 years of age at diagnosis), younger survivors from ALL but not those from solid tumours scored approximately 10 points lower than their older counterparts in the full scale and performance IQs. In the multivariate analysis assessing ages at diagnosis as continuous variables, the only clear-cut impact found was that on global IQ, without significant differences between the verbal and non-verbal performances. This effect most probably resulted from small additive tendencies across all of the tested items. In fact, a negative influence of lower age was observed throughout verbal and non-verbal subtests, without reaching statistical significance. A negative effect of younger age on fine-motor skills, i.e. predominantly on non-verbal performances, has recently been described by Kingma and colleagues [21]. She postulated that this could reflect adverse late effects of vincristine on the peripheral nervous system, which have been widely reported in young children treated for leukaemia [26]. However, Waber and colleagues [27] described the deleterious effects of corticosteroids, especially of dexamethasone, on verbal performances by affecting short-term verbal memory in the setting of high drug concentrations in the hippocampus. As all our patients had been treated with prednisone, and not dexamethasone, such definite effects could not be observed.

The most striking finding of the present study concerned the impressive impact of gender, pointing out a higher susceptibility of the female brain to chemotherapy-induced neurotoxicity. In the univariate analysis, girls with ALL showed distinctly poorer results than boys, both in verbal and nonverbal performances, with about 10 IQ-points less in the full scale, verbal and performance IQ. The percentage of girls with a global IQ under 85 was 3 times higher than of boys.

In the multivariate analysis, gender proved to be the major independent prognostic factor with girls scoring steadily poorer than boys. In seven (four verbal and three non-verbal) of the 11 items of the WISC-R test, the performances of the girls were distinctly lower than those of the boys'.

The prognostic role of sex in the incidence of late neuropsychological deficits after cranial irradiation for ALL has been repeatedly noted in the literature [28,29], girls consistently doing poorer than boys. Waber and colleagues [29] showed in a group of 51 patients with ALL and prophylactic cranial irradiation that 50% of the girls compared with 14% of the boys presented with a full-scale IQ of less than 90. Significant differences were found in both verbal ('Information', 'Vocabulary') and non-verbal ('Block Design') performances. Sex-related differences in long-term neurotoxicity have also been described in children irradiated for brain tumours [30]. Although remaining generally unexplained, these differences suggest that hormonal factors could interact with chemo- or radiotherapy in the development of brain structures, female hormones leading to a higher susceptibility of the CNS [29].

Much less is known in children with ALL treated with chemotherapy-only regimens. In the majority of reports, no sex-specific information can be found. Brown and colleagues [14] recently reported on a modest non-verbal impairment in girls treated for ALL. In the study reported by Kingma and colleagues [21] only slight cognitive impairment was found in the group of children with ALL treated with chemotherapy only and no difference between girls and boys could be recognised. It must be mentioned, however, that the number of patients in the latter study was low: 10 boys and seven girls. Comparing the treatment protocols, especially the drugs, doses and dose intervals used for CNS prophylaxis, no major differences could be found between our and other published studies. Therefore, it remains unclear whether host- or treatment-related factors or both explain the higher sensitivity of the female brain to chemotherapy found here. Further studies with large cohorts of ALL survivors treated without cranial irradiation are needed to confirm or reject our findings. Prospective follow-up of such patients and early neuropsychological rehabilitation of those with cognitive or fine-motor deficits are essential to further improve their chances for successful academic and professional careers.

Acknowledgements

This work has been supported by a grant (Act 255) of the Swiss Cancer League, Cancer Research Switzerland.

References

1. Ries LA, Hankey BF, Miller BA. *Cancer Statistics Review. NIH Publication 91–2789*. Bethesda, National Cancer Institute, 1991.
2. Meadows AT, Gordon J, Massari DJ, Littman P, Fergusson J, Moss K. Declines in IQ scores and cognitive dysfunction in children with acute lymphocytic leukemia treated with cranial irradiation. *Lancet* 1981, **2**, 1015–1022.
3. Rowland JH, Glidewell OJ, Sibley RF, *et al*. Effects of different forms of central nervous system prophylaxis on neuropsychological function in childhood leukemia. *J Clin Oncol* 1984, **2**, 1327–1335.
4. Rowland JH, Glidewell OJ, Sibley RF, *et al*. Effect of cranial radiation (CRT) on neuropsychological function in children with acute lymphocytic leukemia, abstracted. *Am J Pediatr Hematol Oncol* 1984, **6**, 123–128.
5. Roman DD, Sperduto PW. *Neuropsychologicalal effects of cranial radiation: current knowledge and future directions Int J Radiol Oncol Biol Phys* 1995, **31**, 983–998.
6. Madan-Swain A, Brown RT. Cognitive and psycho-social sequelae for children with acute lymphoblastic leukemia and their families. *Clin Psychol Rev* 1991, **11**, 267–294.
7. Anderson V, Smibert E, Ekert H, Godber T. Intellectual, educational, and behavioural sequelae after cranial irradiation and chemotherapy. *Arch Dis Child* 1994, **70**, 476–483.
8. Jankovic M, Brouwers P, Valsecchi MG. Association of 1800 cGy cranial irradiation with intellectual function in children with acute lymphoblastic leukemia. ISPACC. International Study Group on Psycho-social Aspects of Childhood Cancer. *Lancet* 1994, **344**, 224–227.
9. Tsuruda JS, Kortman KE, Bradley WG, *et al*. Radiation effects on cerebral white matter. *Am J Neuroradiol* 1987, **149**, 165–171.
10. Sullivan M, Chen T, Dyment P. Equivalence of intrathecal chemotherapy and radiotherapy as central nervous system prophylaxis in children with acute lymphoblastic leukemia: a Pediatric Oncology Group study. *Blood* 1982, **60**, 948–953.
11. Freeman A, Weinberg V, Brecher M. Comparison of intermediate-dose methotrexate with cranial irradiation for postinduction treatment of acute lymphoblastic leukemia in children. *N Engl J Med* 1983, **308**, 477–481.
12. Valk J, Van der Knaaps MS. Toxic encephalopathy. *Am J Neuroradiol* 1992, **13**, 747–760.
13. Tamaroff M, Miller R, Murphy ML. Immediate and long-term posttherapy neuropsychological performance in children with acute lymphoblastic leukemia treated without central nervous system radiation. *J Pediatr* 1982, **101**, 524–529.
14. Brown RT, Madan-Swain A, Walco GA, Cherrick I, Ievers CE, Conte PM. Cognitive and academic late effects among children previously treated for acute lymphoblastic leukemia receiving chemotherapy as CNS prophylaxis. *J Pediatr Psychol* 1998, **23**, 333–340.
15. Ochs J, Mulhern RK, Fairclough D, Parvey L, Whitaker J, Ch'ien L. Comparison of neuropsychological functioning and clinical indicators of neurotoxicity in longterm survivors of childhood leukemia given cranial irradiation or parenteral methotrexate: a prospective study. *J Clin Oncol* 1991, **1**, 145–151.
16. Mulhern RK, Fairclough D, Ochs J. A prospective comparison of neuropsychological performance of children surviving leukemia who received 18 Gy, 24 Gy or no cranial irradiation. *J Clin Oncol* 1991, **9**, 1348–1356.
17. Mulhern RK, Wassermann AL, Fairclough D, Ochs J. Memory function in disease-free survivors of childhood acute lymphoblastic leukemia given CNS prophylaxis with or without cGy cranial irradiation. *J Clin Oncol* 1800, **6**, 1988 315–320.
18. Giralt J, Ortega JJ, Olive T, Verges R, Forio J, Salvador L. Long-term neuropsychological sequelae of childhood leukemia: comparison of two CNS prophylaxis regimens. *Int J Radiat Oncol Biol Phys* 1992, **24**, 49–53.
19. Copeland DR, Moore BD, Francis DJ, Jaffe N, Culbert SJ. Neuropsychological effects of chemotherapy on children with cancer: a longitudinal study. *J Clin Oncol* 1996, **14**, 2826–2835.
20. Butler RW, Hill JM, Steinherz PG, Meyers PA, Finlay JL. Neuropsychological effects of cranial irradiation, intrathecal methotrexate and systemic methotrexate in childhood cancer. *J Clin Oncol* 1994, **12**, 2621–2629.
21. Kingma A, van Dommelen RI, Mooyaart EL, Wilmink JT, Deelman BG, Kamps WA. Slight cognitive impairment and magnetic resonance imaging abnormalities but normal school levels in children treated for acute lymphoblastic leukemia with chemotherapy only. *J Pediatr* 2001, **139**, 413–420.
22. von der Weid NX, Beck D, Caflisch U, Feldges A, Wyss M, Wagner HP. Standardized assessment of late effects in long-term survivors of childhood cancer in Switzerland. Results of a Swiss Pediatric Oncology Group (SPOG) pilot study. *J Pediatr Hemat/Oncol* 1996, **3**, 383–490.
23. Largo RH, Pfister D, Molinari L, Kundu S, Lipp A, Duc G. Significance of prenatal, perinatal and postnatal factors in the development of AGA preterm infants at five to seven years. *Dev Med Child Neurol* 1989, **31**, 440–456.
24. Wechsler D. *Wechsler Intelligence Scale for Children—Revised*. New York, The Psychological Corporation, 1974.
25. Hüsler J, Zimmermann H. *Statistische Prinzipien für medizinische Projekte*. Bern, Verlag Hans Huber, 1993.

26. Reinders-Messelink HA, Schoemaker MM, Hofte M, Göeken LHN, Kingma A, Van den Briel MM. Fine motor and handwriting problems after treatment for childhood acute lymphoblastic leukemia. *Med Pediatr Oncol* 1996, **27**, 551–555.
27. Waber DP, Carpentieri SC, Klar N, Silverman LB, Schwenn M, Hurwitz CA. Cognitive sequelae in children treated for acute lymphoblastic leukemia with dexamethasone or prednisone. *J Pediatr Hematol/Oncol* 2000, **22**, 206–213.
28. Waber DP, Urion DK, Tarbell NJ, *et al*. Late effects of central nervous system treatment of acute lymphoblastic leukemia in childhood are sex-dependent. *Dev Med Child Neurol* 1990, **32**, 238–248.
29. Waber DP, Tarbell NJ, Kahn CM. The relationship of sex and treatment modality to neuropsychological outcome in childhood acute lymphoblastic leukemia. *J Clin Oncol* 1992, **10**, 810–817.
30. Garcia-Perez A, Sierrasesumaga L, Narbona-Garcia J. Neuropsychologicalal evaluation of children with intra-cranial tumors: impact of treatment modality. *Med Ped Oncol* 1994, **23**, 116–123.