Peer reviewed article

Late effects in long-term survivors of ALL in childhood: experiences from the SPOG late effects study[1]

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Summary

With the use of more intensive regimens including prophylactic CNS treatment, the prognosis of children with ALL has dramatically improved over the last three decades. The aim of this cross-sectional, nationwide study was to comprehensively assess long-term toxicity in ALL survivors, with special attention given to neuropsychological morbidity, and to look for possible differences in cognitive outcome between children having received prophylactic cranial irradiation and those not having received it.

Between 1994 and 1996, long-term survivors of ALL were assessed in a multi-center setting according to a standardized protocol which included, besides usual clinical and laboratory investigations, a comprehensive endocrine work-up. Additionally, children having received anthracyclines were checked for possible late cardio-toxicity with echocardiography and ECG. Intellectual performance was evaluated with standardized neuropsychological tests (age-adapted versions of the Wechsler test).

One-hundred and fifty patients were eligible for the study. The median age at diagnosis was 5 years and at evaluation 16 years, for a median follow-up of 10 years. Thirty-five patients had cranial irradiation as part of the prophylactic CNS treatment. One-hundred and forty (93%) of the 150 eligible patients were completely evaluated in terms of global long-term toxicity: 117 (83%) long-term survivors had no (n = 61) or only minimal (n = 56) late toxicity; 19 (14%) suffered from moderate impairments; 4 (3%) showed severe somatic or neuropsychological sequelae. Intellectual performance could be assessed in 147 (98%) of the 150 eligible patients. The mean global, verbal and non-verbal IQs (103, 105 and 101 respectively) of the ALL survivors as a group were comparable with those found in the general population. The results of the comparison between children having and those not having received prophylactic cranial irradiation showed: 1) significantly higher scores in chemotherapy-only treated patients, both for the global and the verbal performances; 2) significantly poorer results in specific items of the Wechsler test (short-term verbal memory, arithmetics, concentration/speed of processing) in irradiated children.

These findings which show the deleterious role of cranial irradiation correlate well with many other reports found in the literature. However, they could have been influenced by the significantly longer time interval observed between therapy and evaluation in our irradiated patients. Prospective studies are needed to further characterize the potential neuropsychological hazards of chemotherapy and their evolution over time.

Keywords: ALL; childhood; late effects; standardized assessment; neuropsychology

Introduction

As a result of using more intensive treatment protocols, the prognosis of acute lymphoblastic leukemia (ALL) in childhood has dramatically improved over the past 30 years, reaching cure rates of at least 70% [1]. This success rate is attributed to the usage of more intensive systemic (i.e. chemotherapeutic) therapy and to the prophylactic treatment of the central nervous system (CNS) consisting of chemotherapy and/or radiotherapy [2]. With the rising number of long-term survivors, it has become evident that more intensive therapies, especially more efficacious CNS prophylaxis, can induce late toxicities, particularly neuropsychological (cognitive) disabilities [3–7]. If the deleterious role of cranial radiotherapy, especially if given at a younger age and at higher cumulative doses, is well established [8, 9], the potential role of intrathecal and/or intravenous

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chemotherapy (especially methotrexate [MTX]) is less clear. The few prospective studies available seem to indicate that the development of cognitive disabilities increases over time, both after receiving chemotherapy alone and chemo-radiotherapy as CNS prophylaxis, but that there is no clear-cut difference between those children having received prophylactic CNS irradiation and those not having received it [10, 11]. The different results reported in other studies [12–14] may be due to the methodological difficulties and the many pitfalls encountered when assessing neuropsychological disabilities in long-term survivors [15]. Comprehensive studies assessing the whole spectrum of late effects and their global impact on socio-professional insertion of these survivors are still lacking.

Since 1976 the Swiss Pediatric Oncology Group (SPOG) has registered almost every case of childhood ALL in Switzerland and has recorded data relating therapeutic regimens and their outcome. In the early 90's SPOG developed and then checked a standardized set of investigations in a pilot-study [16] to comprehensively assess late effects of childhood cancer on a cross-sectional basis. The nationwide study began in April 1994 in the 8 SPOG institutions. We will focus hereafter on the results attained in the subgroup of ALL long-term survivors, paying special attention to neuropsychological impairments, and also shortly describing the findings in the field of endocrinology, the cardio-pulmonary and digestive systems, as well as secondary malignancies.

Patients and methods

Between April 1994 and May 1996, more than 500 long-term survivors of childhood cancer entered the multicenter, cross-sectional study, of whom 152 had ALL diagnosed between 1.1.1976 and 31.12.1989. To be eligible, patients had to be alive with no evidence of disease for 5 years or more after diagnosis or relapse, and to be off therapy for at least 2 years. Two patients having undergone bone marrow transplantation (BMT) were excluded.

The study protocol had been approved by the local Ethics Committees and informed consent was obtained from each of the 150 study participants. The patients came to the clinic in the morning; medical and psycho-social histories as well as clinical examination were realized and summarized according to the standardized study forms, blood and urine probes were taken. All laboratory investigations (*Appendix I*), including endocrine work-up with the exception of IGF-1 and IGF-BP3 (centralized determination and interpretation in the Unit for paediatric endocrinology at the University Hospital in Geneva) were done and the results interpreted locally. In the afternoon, neuropsychological testing using age- and language-adapted (German, French and Italian) versions of the revised Wechsler Intelligence Test [17] was realized and interpreted by one of the 2 certified paediatric neuro-psychologists specifically enrolled and trained for the Late Effects Study. The evaluation of psycho-social adjustment was based on anamnestical data regarding contact with peers (integration in sport, school, youth groups), partnership, current employment status, insurance questions and, in older patients, marital status and family.

The main characteristics of the patients are summarized in Table 1. One-hundred and thirty-four patients were in CR1, 12 in CR2 (4 each after isolated testicular, isolated CNS or BM relapse) and 4 patients in CR3. Noteworthy, 146 children (97%) were so called "study" patients, i.e. officially enrolled and treated according to standardized protocols: 82 on SPOG, 37 on POG and 7 on old CALGB studies. One-hundred and four children were treated with chemotherapy only, 5 others were given bilateral testicular irradiation for a local relapse and 41 children received prophylactic or therapeutic CNS irradiation (Table 2).

All toxicities found were recorded in a "Summary Sheet" and computerized for further analysis. The global impact of the late effects on the daily life of the patients was scored according to the scale described in Table III of reference 16. Neuropsychological aspects were then studied in more detail, taking only patients (n = 141) who had no CNS involvement and looking for possible differences between children having and those not having received prophylactic CNS irradiation. The Mann-Whitney U-test [18] was used for the statistical analysis of IQ data. A p-value of <0.05 was considered to be statistically significant.

Table 1

Patients characteristics (n = 150 patients; F = 70, M = 80).

ALL phenotypes		
NOS	10	
pre-B cell	132	
T-cell	5	
B-cell	3	
	median	range
Age at diagnosis (yrs)	5.0	0.5–14.5
Age at study (yrs)	16.0	6.5–30.5
Follow-up (yrs)	10.0	5.0–21.5

Table 2

Treatment details (n = 150 patients).

Chemotherapy only, no radiotherapy at all	104 children
Chemotherapy and testicular radiotherapy only	5 children
Chemotherapy and cranial or cranio-spinal radiotherapy	41 children
Cranio-spinal radiotherapy doses:	
conventional fractionation, dose/fraction:	150–200 cGy
total doses:	
patients with cranial radiotherapy only (n = 34):	18–30 Gy (mean 23 Gy)
patients with cranio-spinal radiotherapy (n = 7):	cranial 18–48 Gy (mean 26.5 Gy)
	spinal 18–30 Gy (mean 22.3 Gy)

Results

General data

For 140 (93%) of the 150 ALL long-term survivors complete results were available. The distribution of the overall severity of late effects is summarized in Table 3: 117 (83%) had no (grade 0) or only minimal (grade 1) troubles, not affecting patients' daily lives; 19 (14%) had moderate (grade 2) late toxicity, needing medical attention and/or therapy but not restraining quotidian or professional activities; only 4 (3%) patients were severely (grade 3 or 4) affected. Thus, one of the 4 severely affected patients needed specialized schooling and remained fully institution-dependent as a young adult. This patient had severe measles-encephalitis while on maintenance chemotherapy.

One-hundred and thirty-two (94%) of the 140 survivors went to a normal class, while 6 (4%) needed enrollment in a small-class or extra-tutorial support and 2 (2%) were schooled in a specialized institution. Psycho-social adjustment, as assessed through a short standardized anamnesis looking for age-adapted social insertion (peer-groups, sport, partner, employment, insurance and marital status), was considered adequate in 126 patients (90%), problematic in 12 (8.5%) and poor in 2 (1.5%).

Non-neuropsychological data

The somatic late toxicity effects are summarized in Table 4:

Endocrine problems were found in 20 children (14%); 11 had gonadal dysfunctions: 5 males showed clinical (soft and abnormally small testes) and biological (normal free testosterone by raised FSH levels) signs of isolated exocrine dysfunction and were therefore at high risk of infertility; 2 other boys had clinical (small testes and delayed puberty, retarded bone age) and biological (low testosterone, high FSH and LH levels) signs of global gonadal failure and received testosterone substitution. Five boys had been given bilateral testicular irradiation (18–24 Gy), the others received intensive chemotherapy including cyclophosphamide, one for T-cell and one for mature B-cell ALL. Four girls had persistent (more than 6 months) oligomenorrhoea or amenorrhoea: in 2 cases, a clearcut hypogonadotropic hypogonadism after cranial irradiation (cumulative dose 30–40 Gy) could be demonstrated; one girl developed amenorrhoea after a voluntary drastic diet and weight loss; in the last case, no clear origin could be found. It is noteworthy that 3 survivors (2F, 1M) had a total of 4 absolutely healthy babies.

Seven patients developed growth failure: 4 children had received cranial radiotherapy (24 Gy prophylactic in 3, 30 Gy therapeutic in 1) and presented with evidence of GH-deficiency in both screening tests (low IGF-1 and IGF-BP3) and after insuline-arginine induced hypoglycemia. Two other patients having undergone therapeutic cranio-spinal irradiation remained below –2SD from their expected final height, with distinct disproportionated short stature (sitting height/leg length <1.0). One girl developed an unrecognized, therefore untreated combination of precocious puberty and GH-deficiency after cranial (30 Gy) irradiation.

The last patient with endocrine troubles presented with primary hypothyroidism after cranio-spinal irradiation and was appropriately treated with substitution therapy.

Late *cardio-vascular* toxicity was a rather rare event: 2 asymptomatic patients had echocardiographic signs of left-ventricular cardio-myopathy (WHO grade 1) with slightly reduced shortening-fraction (25–29%) as an isolated finding. Interestingly, both had received moderate cumulative anthracycline doses (270 and 225 mg/m^2 daunorubicine) but belonged to the "oldest" patients in terms of follow-up (15 and 16.5 years after the end of treatment). Arterial hypertension, as defined in (19), was found in 2 long-term survivors: in one, it

Table 3

Global results (n = 140 patients assessed).

Severity score / type	number of patients	percentage
Overall severity of late effects		
0	61	43.5%
1	56	40%
2	19	13.5%
3	3	2%
4	1	1%
Schooling		
Normal class	132	94%
Small class/Extra-tutorial	6	4.5%
Specialized institution	2	1.5%
Psycho-social adjustment (relationships with peers (school, sport, hobbies), partner, job history)		
Normal	126	90%
Problematic	12	8.5%
Poor	2	1.5%

Table 4

Somatic late effects (n = 140 patients assessed).

Endocrine system: n = 20 patients (14%)
Gonadal dysfunctions: n = 11
– 7 males with primary gonadal failure:
5 after bilateral testicular radiotherapy (18–24 Gy) for testicular relapse
2 (1 each with T-cell and mature B-cell ALL) after cyclophosphamide
– 4 females with oligo- or amenorrhea:
2 with hypogonadotropic hypogonadism after cranial radiotherapy
1 with secondary amenorrhea of exogen origin (drastic weight loss)
1 with oligomenorrhea of unknown origin
Primary hypothyreosis: n = 1
– after cranio-spinal radiotherapy; eltroxine substitution.
Growth failure: n = 7
– 4 with GH-deficiency after cranial radiotherapy (24 Gy in 3 and 30 Gy in 1 patient[s])
– 2 patients with GH-deficiency and poor axial vertebral growth after cranio-spinal radiotherapy
– 1 girl with unrecognized pubertas praecox and GH-deficiency after cranial (30 Gy) radiotherapy
Cardio-vascular system: n = 4 patients (3%)
– 2 with cardiomyopathy, WHO grade 1 (SF 25–29%)
– 2 with arterial hypertension (1 of unclear origin, 1 persistent after initial uric acid nephropathy in a T-cell ALL)
Lungs: n = 2 patients (1.5%)
– with restrictive syndrome, WHO grade 2 (VC 65–79% of normal) after severe interstitial pneumopathy (1 VZV, 1 PCP)
Liver and digestive system: n = 3 patients (2%)
– 2 with isolated raised SGPT levels
– 1 with a chronic HCV infection

could be considered idiopathic; in the other, it was clearly secondary to the initial uric acid nephropathy characteristic of T-cell ALL with slight but persistent elevation of serum creatinine.

Pulmonary sequelae were very rarely encountered: 2 asymptomatic patients had a moderate restrictive syndrome (WHO grade 2, VC 65–79% of the normal value), both clearly related to severe interstitial pneumopathy (1 VZV and 1 PCP-infection) during chemotherapy.

Two children had signs of chronic *liver* (MTX-induced?) toxicity (constantly raised SGPT levels), one other suffered from chronic HCV infection and was started on alfa-Interferon therapy.

Of interest, one patient developed a *secondary malignancy* 8.5 years after the diagnosis of common ALL (chemotherapy and prophylactic [24 Gy] cranial irradiation). This girl developed an embryonal rhabdomyosarcoma of the left zygomatic area. She could be salvaged using an aggressive chemo-radiotherapeutic approach. No secondary CNS malignancies were observed.

Table 5

Global intellectual achievement (n = 147 patients assessed).

	mean ± SD	range
global IQ	103 ± 14	68–144
verbal IQ	105 ± 14	68–135
performance IQ	101 ± 14	54–144
Patients with IQ under 85 (<–1 SD)		
global IQ	12/147	8%
performance IQ	13/147	9%
verbal IQ	17/147	11.5%
overall	27/147	18.5%

Neuropsychological data

ALL survivors as a group

Data from 147 out of the 150 patients (98%) were available; 3 patients have been excluded because of absence of data, trisomy 21 and severe PM-retardation (the child with severe measles encephalitis). As shown in Table 5 no differences could be found in terms of global, verbal or non-verbal ("performance") IQ's between ALL survivors as a group and the general population (mean IQ 100, SD ± 15). Also, the proportion of children with learning disabilities (i.e. an IQ under 85) was comparable in both groups (ALL survivors 18.5%, general population 16%, as expected from the normal distribution curve).

Intellectual performances according to the prophylactic CNS treatment

Patients with pre-existing conditions potentially affecting the CNS, as well as patients with leukemic CNS-involvement at diagnosis or later, were excluded from the evaluation. One-hundred and forty-one children and young adults remained eligible: 35 received prophylactic CNS radiotherapy and 106 did not. With the exception of the age at study, which was for historical reasons, higher in irradiated children, no differences were found in the major patients' characteristics, including socio-economic status of the family (SES, see Appendix I) (Table 6, top). All three IQ scores were higher in the non-irradiated children, a statistically significant difference being found both for global and verbal IQ's (Table 6, middle). When looking at

Table 6

Intellectual achievement according to CNS prophylaxis.

	group A (no cranial irradiation)	p	group B (with cranial irradiation)
n	106		35
Age at diagnosis (mean ± SD)	5.6 ± 3.4	n.s.	5.9 ± 3.2
Age at study (mean ± SD)	14.5 ± 4.3	<0.001	21.3 ± 3.4
SES (mean ± SD)	6.9 ± 2.34	n.s.	7.33 ± 2.03
M: F	55: 51 (1.08)	n.s.	20: 15 (1.33)
g IQ (mean ± SD)	105.6 ± 14.4	0.016	99.5 ± 10.7
p IQ (mean ± SD)	106.7 ± 14.4	n.s. (0.09)	102.1 ± 13.8
v IQ (mean ± SD)	103.4 ± 14.0	0.009	96.8 ± 12.4
Patients with IQ under 85 (<–1 SD)			
global IQ	9/106 (8.5%)		4/41 (10%)
performance IQ	7/106 (6.5%)		7/41 (17%)
verbal IQ	10/106 (9.5%)		8/41 (19.5%)

Table 7

Subtle neuropsychological deficits.

	group A	p	group B
DS (mean ± SD)	9.87 ± 2.41	0.007	8.43 ± 2.31
AR (mean ± SD)	10.51 ± 2.88	0.01	9.28 ± 2.50
CO (mean ± SD)	10.53 ± 2.60	0.006	9.03 ± 2.45
BD (mean ± SD)	11.06 ± 3.05	0.51	10.60 ± 2.73

DS = digit dpan; AR = arithmetic's; CO = codes; BD = block design

the subgroup of long-term survivors with IQ's under 85 (Table 6, bottom), no difference in percentage was found between the 2 groups for the global intellectual performances (global IQ 10% vs. 8.5%). However, when looking separately at only verbal or only non-verbal performances, irradiated children were obviously more often diagnosed as "learning-disabled" (19.5% vs. 9.5% for the verbal, 17% vs. 6.5% for the non-verbal performances) compared to their non-irradiated counterparts. The results obtained in each individual item of the Wechsler test were then compared and summarized in Table 7: significantly poorer results in irradiated children were found in arithmetic (AR), short-term verbal memory (digit span, DS) and speed of processing, visuomotor coordination (codes, CO) but not in the 8 other items, as illustrated for block design (BD).

To study the independent impact of cranial radiotherapy, in front of other potential variables influencing cognitive outcome such as sex and length of the follow-up, a multivariate analysis was realized (Table 8). It confirmed that, corrected for gender and follow-up, prophylactic cranial irradiation remained an independent prognostic outcome factor, influencing both global and verbal IQs.

Table 8

Impact of cranial radiotherapy, gender and length of follow-up: multivariate analysis.

Multiple regression analysis

Dependent variable: pIQ

Parameter	Estimate	Standard Error	T Statistic	p value
Constant	109.729	5.53661	19.8188	0.0000
Follow-up	0.296213	0.402483	0.735963	0.4630
Sex	–4.54413	2.32716	–1.95265	0.0529
XRT	–8.2953	3.70572	–2.23851	0.0268

Discussion

Improvement in the survival of children with ALL has been dramatic over the past 30 years. Therefore, the question of long-term performance and eventual sequelae in the biologically cured patients is becoming always more relevant. Due to the small size of the country and to the relatively sedentary population, SPOG was able to register and follow, since 1976, the vast majority (up to almost 90%) of children with ALL in Switzerland [20]. For the same reasons, the group of ALL-survivors assessed in the SPOG Late Effects Study and presented here can be considered to be highly representative, making this study one of the few population-based studies available.

The global results in terms of long-term health-status were encouraging: 84% of all ALL long-term survivors presented no or only minimal late toxicity. Ninety-four percent enjoyed normal schooling and 90% an adequate psycho-social insertion. Life-threatening late effects remained a

rare event: anthracycline-induced cardio-myopathy was found only in 2 of the 140 patients (1.5%) evaluated, after rather moderate cumulative doses (225 and 270 mg/m^2) of daunorubicine. Interestingly, the two affected patients had the longest follow-up (15 and 16.5 years after diagnosis) among the anthracycline-treated subgroup, emphasizing the importance of long-term (life-long?) cardiac monitoring [21, 22]. Late pulmonary toxicity was found in only 2 other patients; in both, a clear-cut relationship was linked to previous severe interstitial pneumopathy while on therapy. In contrast to others [23], we could not observe specific toxicity although the vast majority of our patients (75%) received prolonged low-dose MTX maintenance therapy. It must be borne in mind, however, that based on the recommendations of some authors [24] and the results of our pilot-study [16], pulmonary function tests were not routinely performed.

Having also included patients with relapses (hematological, testicular, CNS), one could expect a relatively high percentage of patients presenting with late endocrine troubles, especially growth failure and gonadal dysfunction. In the vast majority of the cases, the late effects could be related to specific components of the anti-leukemic treatment, as described in the literature: growth hormone (GH) deficiency in patients having received 24 or more Gy cranial irradiation [25]; poor vertebral longitudinal growth resulting in disproportionated short stature [26] after cranio-spinal irradiation (30 or more Gy to the spine), combined precocious puberty and GH-deficiency in a girl with intermediate-dose (30 Gy) cranial radio-therapy [27]; exocrine and endocrine gonadal dysfunctions after testicular irradiation or high cumulative doses of alkylating agents [28, 29].

Neuropsychological (i.e. cognitive) sequelae are of great concern in long-term survivors of childhood ALL. Many papers describe the occurrence of late CNS toxicity caused by both cranial irradiation and i.t. or i.v. chemotherapy, especially MTX (see thereafter).

In the present study, the global intellectual performance of ALL-survivors as a group was comparable to that found in the general population and the same was true for the percentage of patients presenting with learning disabilities (IQ under 85). The mean IQs observed in ALL survivors were not significantly different from those theoretically expected in a random population of healthy Swiss children and adolescents (mean IQ of 100, standard deviation of 15, percentage of learning disabilities (i.e. gIQ <85) (16%).

These objective "psycho-metric" findings were confirmed by the more subjective and "psycho-dynamic" data on schooling and socio-professional achievement.

Only 35 (25%) out of 141 children had been treated with prophylactic CNS irradiation. When analyzing this subgroup separately and comparing the results with the non-irradiated patients, two interesting findings could be observed.

First, irradiated children showed lower IQ scores with a statistically significant difference for both global ($p = 0.016$) and verbal ($p = 0.009$) IQ's. This deleterious effect of cranial irradiation is well described in the literature [8, 9, 30] and is more pronounced the younger the age at treatment. It is noteworthy, however, that all three mean IQ scores of the irradiated children in the present study were in the normal range (gIQ 100, vIQ 97, pIQ 102) indicating no differences, in terms of IQ points, of clinical relevance: a finding also reported in another cross-sectional study [31]. The second important finding was the fact that the proportion of patients with so-called "learning disabilities" (i.e. IQ under 85) was significantly higher in irradiated than in non-irradiated children for both verbal and non-verbal performances: 20% vs. 10%, and 17% vs. 7% respectively. The suspicion of a higher incidence of subtle and specific neuro-psychological deficits in the former group could be confirmed by the study of the individual items of the Wechsler test. In three out of the 11 items, significantly poorer results were found in the irradiated group, with lower scores in arithmetic, short-term verbal memory, visuomotor coordination and speed of processing. Similar results were reported in the study of Ivnik et al. [31] and by other authors [32–35]. These subtle cognitive deficits could be of greater practical relevance, directly affecting the ability to function correctly at school and later in jobs, when memory, concentration and speed of processing become more important and discriminative. These findings are relevant also to the design of interventional strategies at school [36] or professional counseling.

When considering these results, two major aspects should be kept in mind.

First, the prophylactic CNS radiation doses applied to the children of this study were rather high, ranging from 18 to 30 Gy (mean 23 Gy) which is distinctly higher than in the vast majority of currently running ALL protocols typically using 12 Gy whole brain irradiation. Hence, our observations of higher neurotoxicity in irradiated children could be of no relevance for patients enrolled on current treatment protocols which would include prophylactic CNS irradiation. A recently published study from the German BFM group reported no striking cognitive deficiencies in former ALL children treated with 12 Gy prophylactic cranial irradiation [37]. Moreover, another recent paper from a Finnish group found no statistically significant differences either in neurocognitive performances nor in the cerebral glucose metabolism between children with ALL having received or not CNS irradiation [38]. This points out the potential role of the leukemia itself in the developing of late neurocognitive deficits. On the other hand, reports on neurocognitive deficits following chemotherapy-only regimens appear in the literature [39, 40].

Second, the interval between treatment and evaluation was significantly longer in irradiated

children than in non-irradiated ones. This could have been a potentially serious bias, since in both populations studied (but especially in irradiated children) cognitive late effects might become more severe with time [10, 11]. Nevertheless, the multivariate analysis pointed out the role of cranial radiotherapy as a unique independent prognostic factor on global and verbal IQs, when corrected for sex and length of follow-up. Neither gender (although females scored slightly poorer than males in vIQ) nor duration of follow-up showed the same statistically significant impact.

Other insidious long-term effects of cranial irradiation, which have not been reported after chemotherapy-only regimens, like the occurrence of secondary malignant neoplasms of the brain [41] or of the thyroid [42], must be borne in mind when following irradiated survivors of childhood ALL. These observations add weight to the strategy of restricting prophylactic cranial irradiation to children who are at high risk of CNS relapse.

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Appendix I: Standardized assessment protocol

– patient's history (medical and psycho-social)
– standardized clinical investigation, including weight, standing and sitting height, blood pressure, screening audiometry (Phonac®)
– laboratory (CBC, lytes, liver enzymes, glomerular and tubular function)
– endocrinological work-up: Tanner's pubertal status, age at menarche, bone age, fT4, TSH, FSH/LH, free β-oestradiol (females) or free testosterone (males), IGF-1/IGF-BP3
– rest echocardiography and ECG (patients treated with anthracyclines)
– pulmonary function tests (patients with respiratory symptoms)
– neuropsychological evaluation: WISC-R <16 yrs of age, WAIS-R in older patients
– SES (socio-economic status of the family): score based on father's profession and mother's schooling (scale 1-12, a higher score denoting poorer SES)

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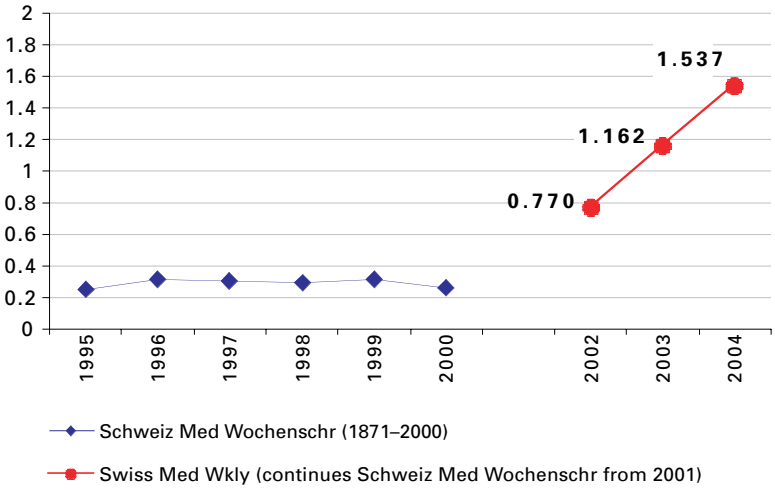

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