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## Association of 1800 cGy cranial irradiation with intellectual function in children with acute lymphoblastic leukaemia

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### Summary

Cranial radiation therapy in childhood acute lymphoblastic leukaemia has been associated with adverse neuropsychological effects, such as low intelligence. However, records show that these associations usually occur when the dose of radiation used is 2400 cGy. We investigated whether a lower dose of 1800 cGy had the same adverse effects on long-term survivors and whether high doses of methotrexate but no radiation therapy would have a more beneficial effect.

We evaluated 203 children for six years in a multi-centre European study. The patients were divided into two groups: 129 children treated with 1800 cGy of cranial radiation therapy and 74 children who received high-dose methotrexate but no radiation therapy. We used full scale intelligence quotient, verbal, and performance IQ tests to assess the patient's intelligence. We found a significant decline in full scale intelligence quotient in the irradiated group that increased with the length of time from diagnosis. Younger age at diagnosis was associated with lower full scale intelligence quotient in the radiated group.

Our results indicate that a radiation dose of 1800 cGy can have negative effects on neurocognitive function and we continue to question the benefit of low-dose cranial radiation therapy.

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### Introduction

Neuropsychological sequelae have been the most extensively studied late effects in long-term survivors of childhood acute lymphoblastic leukaemia (ALL). These late adverse effects follow treatment with preventive central nervous system (CNS) therapy, which can usually include 2400 cGy of cranial radiation therapy with intrathecal chemotherapy. Younger children are much more at risk of developing adverse effects which may only become apparent several years after CNS treatment.<sup>3-8</sup> The severity of these late effects tends to increase with time since diagnosis (or time since first treatment).<sup>9,10</sup>

To minimise the adverse effects of CNS prophylaxis, subsequent treatment protocols have used lower doses of cranial radiation therapy (reduced to 1800 cGy) or have replaced cranial radiation therapy by high-dose methotrexate. Only a few studies have compared the possible adverse effects on patients of having 1800 cGy treatment or no radiation therapy, and such studies have produced conflicting results. These differences may be due to small sample sizes or because of short follow-up.

We evaluated intellectual performance in a large multi-national group of long-term survivors of childhood ALL who received preventive therapy of 1800 cGy and children who received no cranial radiation therapy but who did receive high doses of methotrexate.

### Patients and methods

#### Patients

We studied 203 children who were in continuous first remission of ALL. Patients had stopped therapy for at least 18 months and were aged between 6 and 17. We treated these patients for low or standard risk ALL in 14 paediatric cancer treatment centres in 5 European countries between 1979 and 1988. Few patients refused to participate. Patients who had CNS involvement or prior neurological disease were excluded. The different national treatment protocols included the same drugs in similar schedule rotation and dosage: systemic induction chemotherapy (ranging from 6-10 weeks) with vincristine, steroids, anthracyclines, L-asparaginase, 6-mercaptopurine, and methotrexate (MTX), was followed by a consolidation phase that included CNS preventive therapy.

Our investigation was a retrospective study with a concurrent, non-random control. We found that 2 groups emerged: those treated with cranial irradiation, up to 1800 cGy in 10-12 sessions; n=129 and intrathecal chemotherapy; mostly intrathecal methotrexate, dosage age dependent for a total of 5 or 6 doses, and

	Radiation (n = 129)	No radiation (n = 74)
<b>Gender</b>		
Male/female	58/71	46/28
<b>Age at diagnosis (yrs)</b>	4.3 (2.3)	4.6 (2.7)
Range	0-11.7	0-12.4
<b>Time since diagnosis (yrs)</b>	6.4 (1.6)	5.8 (1.7)
Range	3.6-10.5	2.9-10.6
<b>Age at test (yrs)</b>	10.7 (2.4)	10.4 (2.8)
Range	6-17.0	6-17.0

Table: Patient characteristics

those treated without cranial radiation therapy (n = 74) but with intravenous high-dose methotrexate (2 to 8 g/m<sup>2</sup>) for 4 doses plus intrathecal methotrexate cytarabine and a corticosteroid (triplet, dosage age dependent) for 14 doses.

The protocols usually included a reinduction phase with the same drugs. Systemic maintenance therapy with oral or intramuscular methotrexate plus oral 6-mercaptopurine was followed-up for 24 months.<sup>14,16</sup>

The 2 groups were comparable in gender distribution, age at diagnosis, time since diagnosis, and age at test (table). In this sample, age at diagnosis and time since diagnosis were negatively correlated (r = -0.31).

### Intelligence

All patients were individually assessed with the most recent national standardised form of the Wechsler Intelligence Scale for Children (WISC). We analysed the age-scaled overall summary measure full scale intelligence quotient (FSIQ) as well as its component parts, verbal intelligence quotient (VIQ), and performance intelligence quotient (PIQ).

### Statistics

We statistically analysed our study by applying a general linear model in which the dependent variable FSIQ was related to therapy (cranial radiation therapy: yes or no), time since diagnosis,

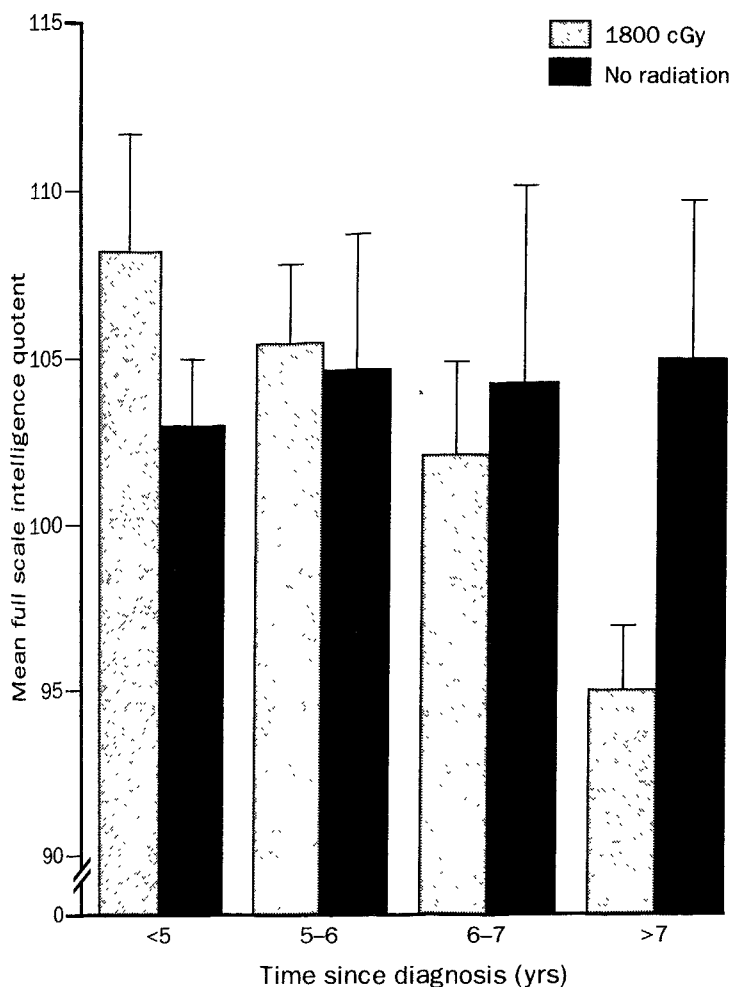


Figure 1: Effects of treatment with 1800 cGy cranial radiation or no radiation therapy on intellectual performance as a function of time since diagnosis

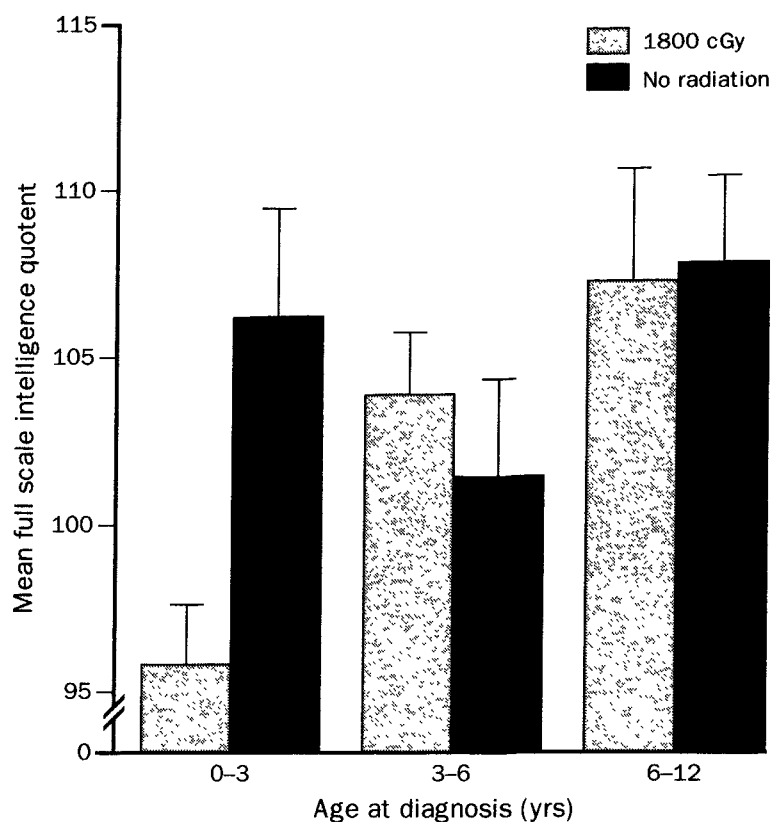


Figure 2: Effects of treatment with 1800 cGy cranial radiation or no radiation therapy on intellectual performance as a function of age at diagnosis

and age at diagnosis. The variables time since and age at diagnosis were analysed separately and the related slopes were estimated. When the interaction of type of treatment with time since diagnosis, or age at diagnosis, was significant, the former effects were evaluated for the irradiated and non-irradiated groups, and the related slopes estimated. Analysis of the effects of radiation or no radiation on intellectual function was done with VIQ, and PIQ. The distribution of radiated versus non-radiated patients was not homogeneous for the different countries which participated in our study.

### Results

#### Time since diagnosis

Figure 1 shows two significant effects; time since diagnosis (F = 9.88, p = 0.002) and cranial irradiation therapy (F = 5.03, p = 0.02). The interaction between time since diagnosis and treatment was significant (F = 6.00; p = 0.02) and indicated that the radiated group showed a significant decline in FSIQ as time since diagnosis became longer (loss of 3.65 [0.83] IQ points per year; p < 0.001). However, in the non-irradiated group, the association with time since diagnosis (-0.45 [1.01]) was not significant. Similar effects were seen when we analysed the component parts of the FSIQ: VIQ (slopes of -3.67 [0.85] in their radiated group versus 0.07 [1.04] in the non-irradiated group) and PIQ (slopes of -2.76 [0.88] vs -1.09 [1.07]).

#### Age at diagnosis

Figure 2 shows the significant effects of age at diagnosis (F = 6.0, p = 0.02) and cranial radiation therapy (F = 4.7, p = 0.03), and the interaction between treatment and age at diagnosis (F = 3.81; p = 0.05). The radiated patients had significantly lower FSIQ's as age at diagnosis became smaller (loss of 1.87 [0.57] IQ points per year; p < 0.001), whereas in the nonirradiated group the slope for age at diagnosis (0.21 [0.64]) was not significantly different from zero. Similar effects were seen when we analysed VIQ (slopes of 1.61 [0.59] vs -0.21 [0.66]) and PIQ (slopes of 1.75 [0.59] vs 0.65 [0.66]).

## Discussion

Our results show that 1800 cGy treatment has negative late effects on neurocognitive function. There were two major findings.

A significant decline in FSIQ after lengthening time from diagnosis was observed only in the irradiated group; and younger age at diagnosis was associated with lower levels of FSIQ in the irradiated group. These effects were also found when analysing VIQ and PIQ separately. The irradiated group had a significant loss of almost 4 IQ points per year since diagnosis, whereas the non-irradiated group did not.

However, we should be cautious when interpreting the size of this decline outside the scope and range of our study. Approximately 80% of patients were between 4 and 8.5 years from diagnosis, so extrapolation outside this range would be an overinterpretation of our data. The main finding is the decline of intelligence in the irradiated group and the difference with the non-irradiated group. We also note that our range of follow-up included the period when other studies indicate that CNS changes become apparent<sup>17</sup> or that declines in IQ occurred, that is 3–7 years after diagnosis and CNS prophylaxis.<sup>8,9,10</sup>

Reports of previous research investigating the effects of 1800 cGy cranial radiation therapy are contradictory. Investigators reported that 1–2 years after cranial radiation therapy they do not see a decline in intelligence.<sup>12,18,19</sup> However, in a longer follow-up, CRT has been associated with significant decreases in intellectual functioning and academic achievement<sup>8,11,13,20</sup> or lower neurocognitive functioning compared with normal.<sup>21</sup>

In a subsequent report, Mulhern et al<sup>22</sup> disagreed suggesting that decreases in IQ,<sup>13,20</sup> which were observed for both the 1800 cGy group and the non-irradiated group on high dose methotrexate, were because of a change in the type of IQ test used. Similarly, Brouwers et al<sup>23</sup> reported there was no decline in IQ after a 3.5 year follow-up. These inconsistencies can be explained by differences in sample selection and inclusion or exclusion of patients with CNS leukaemia or with relapses, but especially by differences in neuropsychological tests, assessment intervals, and small sample sizes.

Younger children are at greater risk for late adverse effects, particularly after a dose of 2400 cGy radiation. Our findings with 1800 cGy are similar to those with 2400 cGy.<sup>1,19,24,25</sup> Younger children at diagnosis were more affected by radiation therapy than older children, whereas age at diagnosis did not affect children who did not have radiation therapy.

CNS preventive therapy for ALL with 2400 cGy and intrathecal chemotherapy has been associated with late adverse effects in the form of histopathological, brain imaging, neuroendocrine, and neuropsychological abnormalities,<sup>26</sup> and with possible secondary malignancy.<sup>27–29</sup> This has led to development of therapy that would be equally protective but less toxic. One approach has been to reduce the dose of cranial irradiation from 2400 to 1800 cGy, and even to 1200 cGy. Our data indicate that 1800 cGy is still associated with negative late effects, even if the magnitude is reduced. A re-evaluation of cranial irradiation in patients not at high risk now seems warranted.

The advantages of our study are that we used only one IQ test, follow-up included the time period when late effects usually become apparent, and the size of our study

population was large compared with previous studies. The limitations are that the two treatment arms were not randomised and that this is not a longitudinal study. However, our two groups were large thus reducing the contribution of chance fluctuations and baseline inequalities to the observed effects.<sup>30</sup> Moreover, the two groups were well matched on most variables, particularly age at diagnosis, time since diagnosis, and age at test.

In conclusion, the results we obtained with our large sample ALL patients who remained in the study many years after diagnosis, indicate a debilitating effect of 1800 cGy on intellectual functioning of long-term survivors.

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