Effect of different doses of prophylactic cranial irradiation in childhood lymphoblastic leukemia on CNS relapse, late cognitive decline and learning disabilities

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Background: Although the need of prophylactic cranial irradiation in childhood ALL protocols has been limited nowadays to high risk patients [1] still the dose of radiation has been controversial due to its late effect on the cognitive functions and learning abilities of those children. When radiation dose was decreased from 2400cGy to 1800 cGy it reduced the neurotoxicity to an acceptable level without decreased efficacy [2]. Newer protocols have studied the decrease of the dose of radiation to 1200cGy [3]. Late effects on pituitary function and growth were also reported by most endocrinologists involved in the follow-up of the cancer survivors [4] Monitoring of therapy-related late effects after ALL therapy in childhood has become an increasingly important area in post-therapeutic patient surveillance. Testing for specific abnormalities in the domains of memory, attention, executive function and visual-spatial skills is recommended. Event-related potentials (ERPs) are recordings of the electric field which the brain produces in fixed time-relation to an event. It uncovers steps of higher brain information processing. The later ERPs’ components (the ‘P300’) index information processing, attention, decisions and language [5,6].

The primary objective of the study was to evaluate the difference between the doses of prophylactic cranial irradiation (1800cGy vs. 1200cGy) as regards central nervous system (CNS) relapse, late cognitive abilities and learning disabilities.

Subjects and Methods: 42 patients treated for acute lymphoblastic leukemia (ALL) and categorized to be at high risk of relapse were assessed. None of the patients had CNS disease at diagnosis. 28 patients received 1800 cGy prophylactic cranial irradiation and 14 received 1200 cGy. All patients received intrathecal methotrexate as well as high dose methotrexate. Visual and auditory P300 studies were carried out after a mean of 4.6 years follow-up. Visual and auditory evoked potentials were done to assess visual and auditory functions at lower brain levels. Selected subscales of Wechsler Intelligence scale for children namely; similarities, vocabulary, picture completion, design, total performance, total verbal and total IQ and arithmetic abilities were applied to both subgroups.

Results: There was no difference in CNS relapse between the two groups (p=0.845). The 1800cGy group showed a significant delay of the visual P300 latency and reduction of the amplitude and delay of auditory P300 latency (p<0.001). In the 1200cGy group only the visual P300 was significantly abnormal (p< 0.001). Psychometric studies showed no significant differences between the 1800cGy /1200cGy subgroups in total IQ and arithmetic abilities. The 1800cGy subgroup showed significantly abnormalities in some subscales namely in similarities, total performance and picture.

Conclusions: Prophylactic whole brain irradiation if given for high risk ALL the recommended dose is 1200cGy due to the lower long term cognitive effect and no difference in the CNS relapse.

Key words: Acute lymphoblastic leukemia, cranial radiation, late effects, relapse
(prednisone-poor response [PPR]), resistance to induction therapy, Age > 12 years, hyperleucocytosis (WBC count > 100,000/microL), T-cell type. None of the patients had CNS disease at diagnosis. All patients received Whole Brain Irradiation (WBI) as part of their treatment protocol.

Twenty eight patients received the first protocol which was an adaptation of the St Jude’s XII ALL protocol in which patients with high risk of relapse received 1800 cGy whole brain irradiation. Fourteen patients received a second protocol which was a local departmental protocol in which the high risk patients received 1200cGy and was characterized by an intensive maintenance where blocks of systemic chemotherapy including Vincristine, Steroids and L-Asparginase was given every 3 months all through the maintenance period. All patients received intrathecal methotrexate (MTX) as well as high dose MTX. The mean total dose of systemic MTX was 12 gm/m2 in protocol A and 10gm/m2 in protocol B and the mean number of intrathecal MTX injections were 12 in both protocols. The minimum follow up period between whole brain irradiation and evaluation was 3 years, mean follow-up was 4.6 years. A control group of 25 age and sex matched normal children was also assessed. All patients enrolled in both protocols who came for follow up at the time of enrolment in the study and their parents accepted to participate in the study and sign an informed consent were enrolled in the study.

**Psychometric studies**
Selected subscales of Wechsler Intelligence scale for children namely; similarities, vocabulary, picture completion, design, total performance, total verbal and total IQ as well as arithmetic abilities subscales were applied to both subgroups as well as the control group.

**Neurophysiologic studies**

**Evoked potentials**
Evoked potential studies were carried out on a digital MEB-9100 Version 0.3-0.6 Neuropack µ (Nihon Kohden, Japan). Two trials for each evoked potential were recorded. The means were registered for statistical analysis.

**Event related potentials (P300)**
Auditory ERPs were carried out using the auditory oddball paradigm. Patients were instructed to raise the right hand as a reaction to the target tone but not the frequent one. The montage used was Cz – linked earlobes. Band pass was 0.5-70 Hz. Stimulus intensity was adjusted at 60 dB above the subject’s hearing threshold. Responses to 30 target and 120 non-target tones were obtained in each trial. The response to the infrequent tone consisted of negative (N100), positive (N200), positive (P300) deflections. P300 latency was measured as the major positive peak after N200. P300 amplitude was measured from N200-P300 peaks. Similarly the visual ERPs were carried out using the visual oddball paradigm by means of goggles. The child received flashes of light in both eyes simultaneously. The child was instructed to raise his finger when a flash is absent unilaterally. Similar waves to those of the auditory ERPs were recorded.

**Visual evoked potentials (VEP’s)**
Pattern reversal VEP’s were carried out using 16’ checker size. Stimulation was binocular at a frequency 1 Hz. Band pass 1-300 Hz. Montage Oz-Fz. P100 wave amplitude and latency were registered.

**Brainstem auditory evoked potentials (BAEP’s)**
BAEP’s were carried out using rarefaction clicks. The stimulation was mono-aural. The montage used was A1-Cz and A2- Cz, Frequency was set at 11Hz and band pass was 1-300 Hz. Stimulus intensity was adjusted at 60 db above the patient’s hearing threshold. Masking of the opposite ear was used and adjusted at 30db below the stimulus intensity. I-III, III-V and I-V wave interpeak latencies were automatically computed. Brain MRI and cytogenetic analysis were not routinely done due to logistic limitation at that time in our centre.

**Statistical method**
The data was coded and entered using the statistical package SPSS version 12. The data was summarized using descriptive statistics: mean and standard deviation for quantitative variables and number and percentage for qualitative values. Statistical differences between groups were tested using Chi Square test for qualitative variables, independent sample t test (student t test) for quantitative normally distributed variables and Nonparametric Mann Whitney test for quantitative variables which are not normally distributed. Correlations were done to test for linear relations between variables. P-values less than or equal to 0.05 were considered statistically significant.

**Results**
Median age at receiving irradiation was 5 years (2-13 years) and 5 years (2-12 years) in the 1200cGy & 1800 cGy groups respectively. Median age at examination was 8 years (5-16 years) and 10 (6-16 years) in the 1200cGy & 1800 cGy groups respectively. Mean follow up period was 4.6 years (3-7 years). Male to female ratio was 1:2 (Table 1).

**CNS relapses**
There was 1/14 patients and 1/28 patients who had CNS relapse in the 1200cGy and 1800cGy groups respectively. There was no significant difference in CNS relapse between the two groups (p=0.854) after a mean follow-up period of 4.6 years.

**Neurophysiologic data**

**Evoked potentials**

**1800 cGy group**
A statistically significant difference was found between
patient and control groups regarding the visual P300 latency (375.0 ± 44.0 ms versus 329.0 ± 16.2 ms respectively, p < 0.001) and amplitude (4.40 ± 1.5 µv, versus 11.0 ± 1.5 µv respectively, p =< 0.001), as well as the VEP amplitude (9.4± 3.2 µv versus 17.24 ± 7.52 µv p = 0.19 respectively).

No significant differences was found between the 2 groups regarding the auditory P300 latency (364.6±77.5ms versus 333.5 ± 14.8 ms respectively, p = 0.06) and amplitude (4.9 ± 2.1 µv, versus 10.8 ± 1.08 µv respectively, p = 0.21). The VEP latency (99.8 ± 3.0 ms versus 99.84 ± 11.0 ms respectively, p =0.9), and the BAEP I-III, III-V, I-V inter-peak latencies (2.1±0.1 ms, 1.9±0.13 ms, 4.0±0.2 ms versus 1.82± 0.24 ms, 2.04±0.4 ms, 3.7±0.1 ms p=0.19, 0.9, 0.8 respectively) showed non-significant differences between the 2 groups as well.

### Psychometric results

Psychometric results showed no significant differences between cases and controls subgroups as regard total IQ and arithmetic abilities. There were significant differences in several subscales between controls and 1800cGy subgroup namely in similarities, total school performance and picture compilation which were not found between controls and 1200cGy subgroup (Table 3).

### Discussion

Prophylactic cranial irradiation in childhood ALL protocols is limited to high risk patients in most treatment protocols. The dose of radiation has been controversial because of its possible late effect on cognitive functions and learning abilities. The St Jude ALL Total Therapy Study XV even omitted prophylactic cranial irradiation at 1800 cGy to be associated with lower full scale IQ, deficits in attention, concentration and ability of sequencing and processing [10]. Some authors even recommended avoiding the strategy favoring prophylactic cranial irradiation [11].

Several previous studies reported defective cognitive functions, attention and memory deficits in children receiving different types of prophylactic protocols for ALL. Delays in the ERPs' P300 latencies and reduction of response amplitudes were mainly reported in irradiated children compared to those receiving protocols that do not include cranial irradiation [12,13,14,15,16]. To the best of our knowledge the comparative long-term detrimental effect of different radiation doses on the cognitive outcome in the long-term survivors of childhood ALL was not previously approached. Event related potentials’ analysis showed a significantly abnormal visual P300 in both 1,800Gys and 1,200cGys groups compared to the controls, the 1,800Gys group showed a further significantly abnormal auditory P300. Defective latency and amplitude of P300 indicate lowered speed of cognitive processing, defective memory as well as impaired attention [17], which was observed in the 1800 cGy group in both higher visual and auditory functions whereas only the higher visual functions were impaired in the 1200 cGy group.

### Table 1. Patients’ characteristics: Rdth: radiotherapy int: intrathecal, MTX: methotrexate, m²: meter square.

| Characteristic                  | Group A (1200cGy) | Group B (1800cGy) |
|--------------------------------|------------------|------------------|
| no                            | 14               | 28               |
| Males/Females                 | 4/10             | 9/19             |
| Median age at Rdth            | 5 (2-13)         | 5 (2-12)         |
| Median age at evaluation      | 8 (5-16)         | 10 (6-16)        |
| prednisone-poor response      | 6                | 12               |
| resistance to induction therapy | 1               | 2                |
| WBC count >100,000/microL     | 6                | 8                |
| T Cell Immunophenotype        | 4                | 7                |
| Mean no of int MTX injections | 12 (6-14)        | 12 (6-14)        |
| Mean dose of MTX received/m² | 12 gm            | 10 gm            |

### Table 2. Relation between P300 and Radiation dose. AP3 L: auditory P 300 latency, AP3 A: auditory P 300 amplitude, VP3 L: visual P 300 latency, VP3 A: visual P 300 amplitude.

| Control               | High dose /control | Low dose /control |
|-----------------------|--------------------|------------------|
|                        | Ms                 | p value          | Ms               | p value          |
| Wave I-III            | 1.82±0.24          | <0.001           | 2.1±0.1          | 0.19             |
| Wave III-V            | 2.04±0.44          | 0.09             | 1.9±0.13         | 0.90             |
| Wave I-V              | 3.7±0.183          | <0.001           | 4.0±0.02         | 0.89             |
| VEP L                 | 99.8±11.07         | 0.55             | 99.8±3.0         | 0.9              |
| VEP A                 | 17.2±7.52          | <0.001           | 9.4±3.2          | 0.19             |
| AP3 L                 | 333.5±14.8         | <0.001           | 364.6±77.5       | 0.06             |
| AP3 A                 | 10.8±10.8          | 0.08             | 4.9±2.1          | 0.21             |
| VP3 L                 | 329.0±16.2         | <0.001           | 375.0±44.0       | 0.001            |
| VP3 A                 | 11.0±1.5           | <0.001           | 4.4±1.5          | <0.001           |

### Table 3. Psychometric results.

| Test                  | P-value Group A versus Control | P-value Group B versus Control |
|-----------------------|--------------------------------|--------------------------------|
| Total verbal          | 0.456                          | 0.886                          |
| Total performance     | 0.697                          | 0.004                          |
| similarities          | 0.095                          | 0.042                          |
| Arithmetic abilities  | 0.567                          | 0.075                          |
| Picture compilation   | 0.766                          | 0.001                          |
impaired in the 1200 cGy group. This was reflected on some psychomotor abilities of those children especially total school performance, picture compilation and similarities in the 1800cGy group.

These findings indicate a more extensive impairment of the intellectual abilities in the subgroup receiving 1800cGy compared to the controls which was much less in the subgroup receiving 1200cGy at no significant increased protection from CNS relapse. 1800cGy irradiation was furthermore associated with defective transmission along the auditory pathways not only at the cortical level but down to the level of the Pons and medulla as indicated by the highly significant elongation of wave I-III, III- V & I-V inter-peak intervals. The visual cortex and the retinocortical transmission however expressed a vulnerability to irradiation. Significantly reduced VEP amplitudes were reported in both groups denoting axonal damage within the visual pathways. This further explains the more obvious cognitive decline in the 1800c Gys group since irradiation injury extends not only to the higher intellectual cortical functions but also to both the auditory and visual sensory processing at lower brain levels within that group. Previous studies reported sub-clinical minor CNS changes mainly involving the visual [18,17] and auditory pathways [12] in the form of demyelinating lesions causing delay of the P100 wave latency and inter-latencies of waves I-III, I-IV and III-V respectively even in absence of symptoms. Radiation was accused to be the cause of white mater disturbances [20] regardless of the dose. Delays of the VEP were reported in patients who received 2400cGy [19] as well as 1800 Gys. Such delays were reported mainly in irradiated patients and not in those who received only chemotherapy [20,21,22]. These significant delays encouraged some authors to recommend the use of VEP latency as a tool to monitor brain radiation side effects [23]. Recent studies which evaluated the cognitive outcomes of chemotherapy treatment without radiation therapy using the St Jude ALL Total Therapy Study XV showed a significantly higher risk for below-average performance specially in patients receiving higher doses of systemic chemotherapy and concluded that omitting cranial irradiation may help preserve global cognitive abilities, but treatment with chemotherapy alone is not without risks [9].

Conclusion

Prophylactic whole brain irradiation if given for high risk ALL the recommended dose is 1200cGy due to the lower long term cognitive effect and no difference in the CNS relapse.

Competing interests

MM, NS and MN were involved in the design and conduct of the study and the interpretation of the data and the preparation of this manuscript. RA was involved in the statistical output as well as the interpretation of the data and the preparation of this manuscript. None of the other authors have any conflicts of interest to declare.

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