

## RESEARCH COMMUNICATION

# Intellectual and Behavioral Impairment after Chemotherapy and Radiotherapy among Children with Cancer in Iran

Susan Parsay<sup>1\*</sup>, Alireza Mosavi-Jarrahi<sup>1,2</sup>, Fariba Arabgol<sup>3</sup>, Azadeh Kiomarcy<sup>1</sup>

### Abstract

**Objective:** It is well established that treatment modalities against cancer have psychosocial and serious medical side effects especially neurologic, learning, and intellectual disorders among children with cancer. The aim of this study was to evaluate the behavioral change specially the effect of chemotherapy and cranial radiotherapy on the development of attention deficit hyperactivity disorder (ADHD) in children with cancer.

**Materials and Methods:** The children diagnosed with cancer and referred to Mahak Hospital (a well funded charity organization helping children with cancer in Iran) participated in this study. To assess the post treatment behavior, the Conner's Rating Scales (CRS) questionnaire, which its reliability and validity has been well established was administrated by trained interviewer in a two hour sessions to mother or attending nurses of the cases. The relationship between attention deficits, hyperactivity disorder were assessed with different categories of treatment, socio-economic status, age at diagnosis, sex, as well as duration since treatment. **Results:** During periods of six months, 30 subjects (16 male and 14 female) were studied and participated in the study. Fifteen cases had both radiotherapy as well as chemotherapy and 15 cases just had chemotherapy as their treatment regiment. The mean Conner's Rating Score (total score of ADHD) were higher among those who received both chemotherapy and radiotherapy compared with those who had just chemotherapy but it was not statistically significant ( $34.7 \pm 12.6$  for just chemotherapy and  $39.3 \pm 9.0$  for chemo and radiotherapy together). The total Conner's Rating Score was higher among girls compared to boys (mean  $\pm$  standard deviation was  $39.8 \pm 9.4$  for girls and  $33.7 \pm 12$  for boys). Duration since treatment, age diagnosis, and mother's level of education had effect in post treatment intellectual capacity and behavioral aspect of patients. **Conclusion:** In the light of dramatic improvement of survival among children with cancer the intellectual and behavioral impairment due to treatment modalities needs serious attention and proper medical management.

**Keywords:** Childhood cancer - attention deficit - hyperactivity disorder - Conner's rating scale - Iran

*Asian Pacific J Cancer Prev*, 12, 1329-1332

### Introduction

Up to early 1970, children who were diagnosed with acute lymphoblastic leukemia had a life expectancy of about one year. In most cases the reason of death among them wasn't due to the leukemia itself but due to its consequences on the central nervous system (Stehbens et al., 1991). Administration of Intra spinal methotrexate and utilization of cranial radiotherapy as part of their treatment considerably prolonged the life span of these patients. At present the five years survival is almost 70% (Peckham, 1991). Though this treatment regimen improved survival dramatically, however, its long term side effects especially the neuropathogenesis and post treatment psycho-behaviors impairment are now new challenges facing scientist in the field of childhood cancer.

Histological and radiologic studies show that two types of delayed neuropathologies including leuko-encephalopathy and mineralizing micro encephalopathy

are the consequences of cranial radiotherapy (Price and Jamieson, 1975). The pathological sequel occur normally after a few months of radiotherapy and are manifested around the basal ganglia, by means of demyelization, dilation of ventricles and calcification of the brain tissue (Tsuruda et al., 1987). The clinical symptoms that manifest as a response to this tissue damages are seizure, and ataxia that are also directly proportional to the dose of cranial radiotherapy. Studies of subject undergoing extensive chemo and radiotherapy have shown that there is a direct relation between the type and severity of neuropsychological damage to the extent of brain damage (calcification around the basal ganglia, specifically in the caudate lobe area (Marsden, 1982; Brouwers et al., 1985).

In addition to somatic adverse effect of radiotherapy; the psychological impairment of recipients of chemo and radiotherapy has been documented as difficulties in nonverbal tasks, fine movements, special cognition, and sensory movement function. Serious disabilities have also

<sup>1</sup>Dept. of Public Health and Social Medicine, <sup>3</sup>Department of Child and Adolescent Psychiatry Medical School, Shaheed Beheshti University of Medical Sciences, <sup>2</sup>Cancer Research Center of the Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran \*For correspondence : Fall1347@yahoo.com

been reported in the fields of attention disturbance and concentration and learning capabilities (Eiser, 1980). The behavioral change and psychosomatic effect of diagnosis of leukemia in a child along with a multitude of other therapy related stresses such as hospitalization, separation from home and family, long term medical treatment, absence from school, etc, which consequently cause depression, anxiety, low self confidence, and a decline in academic performance (complication that normally are underestimated in the light of ALL diagnosis).

The aim of this research was to evaluate the behavioral change specially the effect of chemotherapy and especially cranial radiotherapy on the development of ADHD in children with ALL diagnosis.

## Materials and Methods

The children participated in this study represent a group of patients referred to Mahak Hospital, a tertiary hospital providing comprehensive pediatric oncology services to children all over the country as well as childhood cancer patients referred by the United Nation refugee commission (<http://www.mahak-charity.org>). The hospital provides all lines of treatment as well as hostelling and hospice to referred patients. For the purpose of this study the families of subjects were contacted by resident nurse to participate in the study, and required to provide written, informed consent prior to their inclusion in the study. The study was approved by the ethical committee. Subjects with known psych-behavior symptoms were excluded from the study.

To assess the post treatment behavior, the Conners' Rating Scales (CRS), which were developed primarily for use in drug studies of children with hyperkinesias (Goyette et al., 1978) was used to assess attention deficit (AD) and hyperactivity disorder (HD and summing AD and HD as total score (ADHD). The reliability and validity the CRS are well established and has been demonstrated in different studies in several populations (Conners, 1998). For the purpose this study, the CRS questionnaire was administrated by trained interviewer in a two hour sessions. Mother or attending nurse was the interviewee. The relationship between attention deficit, hyperactivity and both AD and HD together as the total score were compared among different categories of treatment, socio-economic status (measured as the educational level of mother), age at diagnosis, sex, as well as duration since treatment.

Mean of the scores were compared between different groups using Students't-test with 0.05 as statistically significant level. Data were analyzed using Microsoft Excel and SPSS version 16.

## Results

During periods of six months, 30 subjects (16 male and 14 female) were studied and participated in the study. The mean  $\pm$  standard deviation age at diagnosis was  $7.6 \pm 3.4$  with no major differences among the two sexes. Sixteen cases (53%) suffered acute lymphocytic leukemia and 14 suffered other kinds of childhood cancer

(Table 1). Fifteen cases had both radiotherapy as well as chemotherapy and 15 cases just had chemotherapy. The mean total score (ADHD) were higher among those who received both chemo and radiotherapy compared with those who had just chemo therapy but it was not statistically significant. The same finding was seen for hyperactivity score but not for attention deficit (Table 2). Comparing ALL cases with other patients, the mean total score was lower for ALL patients (mean  $\pm$  standard deviation of  $34 \pm 10$ ) compared with other patients (mean  $\pm$  standard deviation of  $41 \pm 11$ ). The total score was higher among boys compared to girls (mean  $\pm$  standard deviation was  $40 \pm 9$  for boys and  $34 \pm 12$  for girls). Duration since treatment differed among subjects with few subjects having duration since treatment more than three years and the resting less than one year with median duration of 12 months. There were no major differences in scores of, attention deficit, and hyperactivity or both between the two categories of duration since treatment (Table 3). The age was categorized into less than and equal to 5 years more than 5 years. There was a slight difference in attention deficit between the two age group with the age less than 5 having lower score compared to age more than 5 (table 3). There was slight differences in scores between sexes with female scoring higher in both AD and HD as well as total score (Table 3). Except few mother with higher education whose children scored high in total score,

**Table 1. Frequency of Cancer Type among the Cases**

Cancer Type	Frequency	Percentage
Acute Lymphocytic Leukemia	16	53.3
Brain Tumor	4	13.3
Lymphoma	3	10.0
PENET	2	6.7
Retinoblastoma	2	6.7
Sarcoma	3	10.0
Total	30	100

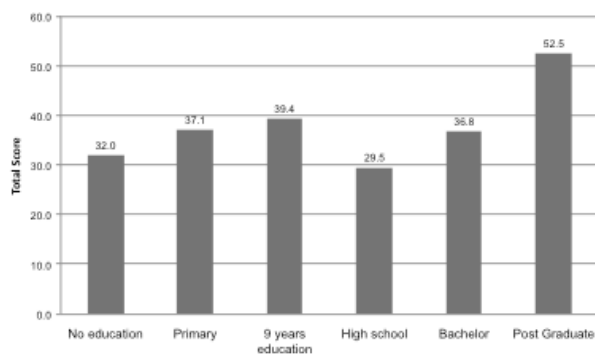
**Table 2. Post-treatment Psycho-behavior Symptoms for the Two Treatment Regiments**

Symptoms	Chemotherapy alone	Chemotherapy plus radiotherapy	P-Value
Hyper Sensitivity	17.7 $\pm$ 7.3*	22.6 $\pm$ 8.4	0.09
Attention deficit	17.2 $\pm$ 7.2	16.7 $\pm$ 4.8	0.26
Total Scores	34.7 $\pm$ 12.6	39.3 $\pm$ 9.0	0.81

\*Mean  $\pm$  Standard deviation

**Table 3. Post-treatment Psycho-behavior Symptoms for Age Group, Duration after Treatment, and Gender**

	Number	Total Score	Attention Deficiency	Hyperactivity Disorder
Age group				
$\leq 5$	11	35.5 $\pm$ 13.3	14.5 $\pm$ 6.6	21.2 $\pm$ 9.5
$> 5$	19	37.9 $\pm$ 9.7	18.3 $\pm$ 5.5	19.5 $\pm$ 7.5
Duration since treatment				
$< 12$	20	36.4 $\pm$ 12.1	17.1 $\pm$ 6.8	19.4 $\pm$ 7.6
$> 12$	10	38.3 $\pm$ 8.8	16.7 $\pm$ 5.0	21.6 $\pm$ 9.2
Gender				
Male	16	18.1 $\pm$ 8.8	15.7 $\pm$ 6.6	33.7 $\pm$ 12.0
Female	14	21.8 $\pm$ 7.2	18.0 $\pm$ 5.7	39.8 $\pm$ 9.4



**Figure 1. Distribution of Conner's Rating Scale across Level of Mothers Education**

mother's education did not associated with the achieved score by their kids (Figure 1).

## Discussion

Our study showed that chemotherapy as well as radiotherapy can affect the psycho-behavior of children with cancer after treatment with more adverse effect among those underwent radiotherapy. Annually 1% of children are newly diagnosed with cancer, they receive radiation and chemotherapy or surgery according to the diagnosed cancer and recommended standard treatment (Stehbens et al., 1991). Childhood cancers have different prognosis and treatment outcomes compared to cancers of adults. The most common cancers among children are leukemia, Hodgkin's lymphoma, non Hodgkin's lymphoma, CNS tumors, Sarcoma, Nephroblastoma and retinoblastoma, respectively (Howard et al., 2008). The distribution of kind of cancer among our study resembles the same distribution as other population with acute lymphoblastic leukemia as the most frequent cancer among children. Before the utilization of chemotherapy in 1948, the survival period of child diagnosed with ALL was a mere 2 or 3 months, but today their five years survival rate has increased to almost 80% (Pui et al., 2004).

It is well established that treatment modalities against cancer has its psychosocial and serious medical side effects. The administration of chemotherapy causes different side effect among children that vary from one patient to another. The most common side effects are hair loss, inflammation and ulceration of the gums, nausea, vomiting, diarrhea, polyuria, and sometimes constipation, thirst, pigmentation of skin, menopause, general weakness, drowsiness and injection site related problems. Depression, sorrow, fear of rejection and being invert are also some of the psychological manifestations of chemotherapy, which can later on lead to impaired social interaction (Reddick et al., 2005). Radiotherapy, although has lesser acute side effects than chemotherapy, the side effects radiotherapy are manifested much more later in the child's life span especially children who undergo cranial radiotherapy succumb to neurologic disorders, learning disorders as well as a range different medical side effect as infertility.

According to the latest research sources, the after effects of chemotherapy manifest almost a decade after the discontinuation of treatment, and thus explains as to

why the patient complains of these symptoms many years later (Myers, 2009).

Studies have shown that brain metabolism is impaired after chemotherapy, which may also lead to impaired memory capacity and inability to carry out complex tasks (Myers, 2009). Almost a quarter of the patients who received chemotherapy have reported to have impaired brain function, and also complained of short attention span (Patel et al., 2009). In a very recent research it has been cited that high percent of the patients experienced impairments, such as a attention span, concentration, school performance and executive functioning, with experiencing certain problems as carrying out simple tasks. Studies also show that in patients who received chemotherapy, had decreased metabolism rate in areas associated with memory (Costa, 2010).

Children who were diagnosed with ALL, and later successfully cured, had increased cognitive impairment. This was identified as a decrease in their intelligence quotient (IQ), or decline in their academic performance evaluated through concentration, memory and speed of information processing (Schatz et al., 2000). Recently studied has documented damage to brain white matter causing decrease in brain processing capability (Reddick et al., 2005). Interpretations of sono-imaging techniques such as MRI and CT-Scan have shown that in children who have survived brain tumors after receiving cranial radiotherapy, there was an abnormal growth in brain's white matter (Reddick et al., 2003).

Neuropsychological studies show that survivors of ALL who received prophylactic cranial radiotherapy experienced a considerable decline in their Intelligent Quotient (IQ) in comparison to the control group (Butler et al., 1994). This is compatible with our finding that cases who had both chemo and radiotherapy score higher in their ADHD. Another study measuring the IQ of children receiving high doses of radiation had impaired IQ with female having greater risk compared with male (Waber et al., 1992; Smibert et al., 1996) our finding is compatible with this fact that females suffer more compared with males.

In conclusion: our study demonstrate that post treatment complication of intellectual and behavioral impairment needs due attention and with the fact that the disease free survival improves this impairment needs further care and management.

## Acknowledgment

The investigators appreciate the efforts, recourses, and the help that the Mahak Charity Organization (<http://www.mahak-charity.org>) provide toward achieving the aim of this study.

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