

Brain size and neuropsychological functioning in long-term survivors of pediatric acute lymphoblastic leukemia

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Abstract: With the increased survival of pediatric cancer patients the interest in the late effects of treatments is rapidly increasing. Long-term survival rates for children with acute lymphoblastic leukemia (ALL) now approach 90%. Treatment for ALL includes intensified central nervous system (CNS)-directed therapy, which is associated with risks for long-term neurocognitive effects. It is becoming clear that current therapies can have not only a detrimental effect on IQ, processing speed, and memory, but also on structural changes that lead to permanent alterations of the organization of the CNS. Understanding how the CNS is affected by the treatments is a critical step in evaluating current therapies and developing interventions to decrease the incidence and severity of long-term changes in brain anatomy and function.

Keywords: Acute lymphoblastic leukemia (ALL); late effects; neuropsychology

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The numbers of annual publications on the *late effects of cancer treatment* have increased steadily over the past several decades. In the early 1980's just over 100 articles a year were published on this topic. Fast-forward to 2012 and close to 900 articles can be found looking at the same issues. This is not surprising and is a byproduct of the success of Cancer Medicine. With advancements in therapy, more patients are surviving and living with the long-term consequences of the medications and procedures used to cure their cancer. This is especially important in pediatric cancer survivors who are often diagnosed at a young age and therefore have a much longer span of time in which to be concerned with late effects of therapy. If a child is diagnosed with cancer when they are five years old and truly "cured", their survival should be similar to that of other five years old and they should have 70-80 years of life remaining. Thus, a key question is what are the long-term consequences of their cancer and its treatment, with substantial interest on long-term changes that may occur in brain anatomy, intellect, neurocognitive and neuropsychological function.

Zeller and colleagues from Oslo recently published a

study, *Reduced Neuroanatomic Volumes in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia*, in the *Journal of Clinical Oncology* that addresses these issues in survivors of childhood acute lymphoblastic leukemia (ALL) (1). ALL is the most common cancer that occurs in children, accounting for 25-30% of all malignancies that occur before age 15-20 years. Treatment of childhood ALL is one of the major successes in Cancer Medicine, with long-term survival rates increasing from about 10% in the late 1960s to about 90% today (2). A key part of these improved outcomes was the recognition that ALL therapy must include treatment directed at lymphoblasts in the central nervous system (CNS). As Zeller points out, over time there has been a reduction in the use of CNS radiation, but intensive CNS directed chemotherapy, including intrathecal (IT) chemotherapy and intensive systemic chemotherapy, is essential for cure. It is well established that chemotherapy alone can have significant negative neurocognitive effects for these patients (3). The intensity of IT chemotherapy is clearly not the only determinant of late effects, as one study showed that neurocognitive functioning was

similarly impaired in patients who received single drug treatment with IT methotrexate or triple IT therapy with methotrexate, cytarabine and hydrocortisone (4).

Although it is accepted that chemotherapy is having these effects, the mechanism of actions is not entirely clear. One theory of action causing these effects is that chemotherapy results in oxidative stress in the CNS with one study showing that measurements of increased oxidative stress in the CSF are associated with decreased executive function in ALL patients two years after the start of therapy (5). Additional studies have shown that changes in the phospholipid makeup of the white matter (WM) of the CNS can be detected in ALL patients and these patients had an association between level of sphingomyelin levels and motor speed up to three years following diagnosis (6). Other groups have looked at the role of genetics in the late effects of chemotherapy on patients. Studies have also started to find the importance of genetic polymorphisms in ALL patients and their response to chemotherapy, particularly related to CNS effects and neurocognitive outcomes (6,7). Zeller *et al.* continue to add to this knowledge by helping to understand how these effects may be occurring with underlying structural changes in CNS neuroanatomy.

The idea that survivors of ALL have smaller WM volumes is not new, but the authors have expanded beyond looking at just WM and shown that these survivors show a loss of cortical grey matter (GM) as well. They were also able to delve deeper into the CNS and look at specific structures of the brain. One important finding included smaller volume sizes of the caudate in survivors compared to controls. The caudate is associated with learning and memory as well as with problem solving and verbal skills. These findings match well with the author's own findings of decreased processing speed, executive function and verbal learning in survivors compared to controls as well as in previously published data (3). In their global view of the CNS, the finding of an overall reduced intracranial volume in ALL survivors compared to controls also supports the overall effect chemotherapy is having on the brain.

One of the major difficulties in studying the late neurocognitive effects of cancer treatment is the difficulty of obtaining a large cohort of patients to follow and evaluate. This is highlighted in the comprehensive review of available studies by Anderson and Kunin-Batson, where the largest cohort of ALL survivors included for neuropsychological assessment was 47 (3). In this single study, Zeller *et al.* were able to test more than 2.5 times the number of ALL survivors with an equal number of controls. It allowed

them to not only analyze the data as a large group, but also perform subset analyses excluding patients who had received CNS radiation and comparing subgroups such as those with varying education levels to ensure their results were not biased by treatments or other factors. The fact that their conclusions persisted across subgroup analysis adds confidence in their findings.

There are a number of unique strengths of this cohort. The authors studied 138 of 353 (39%) survivors among 538 children younger than 16 years old diagnosed with ALL between 1970 and 2002 and treated at a single hospital in Oslo (which treats about half of pediatric cancer patients in Norway). Unlike most studies that extend back to 1970, only 13.8% of children received cranial irradiation and only 2.3% underwent stem cell transplantation. Thus, by and large, the effects observed are those of systemic and IT chemotherapy. Similar to the therapy used by many European groups, patients received only a modest number of IT treatments (median 8-14) compared to 20-30 IT chemotherapy doses included in many North American ALL regimens. One of the most notable aspects of the therapy received was the large cumulative dose of corticosteroids, with a median cumulative prednisone dose of 4,000-6,000 mg/m²! This is similar to doses used by other groups and may be a very important determinant of long-term CNS anatomical changes and function. Also of note is that the cumulative systemic dose of intravenous methotrexate increased substantially over the period of study, from a median of 1,500 mg/m² in the 1970-1981 cohort to 40,000 mg/m² in the 1992-2002 cohort.

A very important characteristic of this cohort is that, despite observed changes in CNS neuroanatomy and neuropsychological functioning, the IQ of patients was above average decades after therapy (median 114) and was no different from that of age-matched controls. Despite this, the impressive long-term follow-up of this cohort (median 22.5 years, range, 7.4-40 years) clearly establishes that the structural changes described are true long-term, permanent alterations of the CNS. These structural changes were associated with demonstrative statistically significant decrements in the results of neuropsychological test results, particularly in processing speed, executive function, and verbal learning and memory. These findings challenge pediatric oncologists and all health care professionals that treat childhood ALL survivors to develop interventions to decrease the incidence and severity of these long-term changes in brain anatomy and function.

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Footnote

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