Implications of 25-Year Follow-Up of White Matter Integrity and Neurocognitive Function of Childhood Leukemia Survivors: A Wake-Up Call

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Improved treatment via new drug development, combination therapy, and methods of treatment have resulted in 73% to 80% of children treated for acute lymphoblastic leukemia (ALL) being considered long-term survivors who are cured. This survival rate has not come without a cost, with long-term consequences (late effects) occurring in reproductive capacity, cardiac function, neurocognitive function, endocrine function, pulmonary function, and second malignancy related to treatment. As children survive longer into adulthood, an additional late effect is beginning to be recognized: an onset of diseases associated with aging occurring earlier than in the general population. Though much is known about neurocognitive late effects in children and adolescents during school-age and adolescence, nothing is known about the long-term effects of treatment received during childhood on the survivors of ALL 20 to 30 years after diagnosis.

In the article accompanying this editorial, Schuitema et al describe one of the first studies in this area, and the results are consistent with other late-effects studies related to early aging concerns. Ninety-three young adults treated between 1978 and 1990 for childhood ALL with either cranial radiation therapy (CRT) or CNS prophylaxis with chemotherapy were evaluated using magnetic resonance imaging (MRI) and standardized tests of neurocognitive function. Survivors who were treated with CRT had significantly reduced white-matter integrity, as measured by MRI fractional anisotropy (FA), and poorer neurocognitive function (lower intelligence quotient, poorer visuomotor accuracy, stability, and sequential working memory, and poorer work flow during sustained attention). Decreases in FA were observed in chemotherapy-only patients, but those decreases were more moderate in CRT-treated survivors. Consistent with other reports describing white-matter integrity during childhood and adolescence, younger patient age at the time of CRT and higher dose were associated with worse white-matter integrity. Steep declines in FA in the frontal and parietal white matter were observed related to age of assessment, suggesting an accelerated pattern of aging. To emphasize this point, the authors note anatomic similarities between these long-term ALL survivors and aging patients with cognitive decline or dementia.

Accelerated aging of the CNS is a concern of late-effects investigators. Evidence is growing for persistent neurocognitive impairment after both CRT and systemic chemotherapy in survivors of cancers involving treatment of the CNS with CRT, chemotherapy, or combination CRT and chemotherapy. Impairment is most frequently seen in the areas of executive function, processing speed, and short-term or working memory. There is additional risk for increased severity in other areas of cognitive function in children who are younger at time of treatment or who receive higher doses of CRT. For children, school performance is often negatively affected; little is known about daily-function challenges in adult survivors.

Treatment of childhood ALL has changed dramatically over the last 30 years, particularly CNS prophylaxis. Before 1985, with the introduction of Pediatric Oncology Group 8602 study, children with B-lineage or T-lineage ALL were typically treated with craniospinal radiation therapy, sometimes alone and sometimes in combination with intrathecal methotrexate. The dose of CRT was typically 24 Gy or 18 Gy. The Pediatric Oncology Group 8602 study eliminated CRT for the majority of children treated for ALL, replacing it with intrathecal methotrexate or triple intrathecal chemotherapy (methotrexate, cytarabine, and hydrocortisone). This strategy reduced some of the neuroendocrine and growth delays that had been associated with CRT, but neurocognitive deficits were still observed 3 or more years after diagnosis. Treatment for ALL since the early 1990s has included a more aggressive use of systemic methotrexate during the consolidation phase of therapy, increasing from 1 gm/m² to 5 gms/m². This change, without CRT, has also resulted in reports of increased neurocognitive impairment and computed tomography and MRI evidence of primarily calcification in the CNS.

For children with CNS tumors, CRT remains the backbone of therapy after surgical resection. CRT doses are typically much higher than those used in the historical and current treatment of ALL (30 Gy to 65 Gy v 18Gy or less). There have been efforts dating back to the mid-1980s to reduce the dose of CRT delay its use, or eliminate it from treatment, but most children with high-grade malignant CNS tumors will likely be treated with CRT, either photon-beam or proton-beam.
Although CRT for CNS prophylaxis in children with ALL is now infrequently used, and use of CRT is being minimized whenever possible for children with CNS tumors, a significant number of children are still receiving primary or prophylactic treatment of the CNS with CRT in doses similar to or higher than those used for the patients followed by Schuitema et al. Given their results, this raises a significant concern about the long-term CNS and neurocognitive integrity (20-, 30-, or 40-year effects) for children who have been treated with CRT over the last 40 years, as well as those currently being treated. Further, while not as striking as the CRT results, Schuitema et al also report declines in FA and neurocognitive function in patients who had intrathecal chemotherapy only. CNS prophylaxis combined with increasing doses of systemic methotrexate has intensified over the last 20 years, with reported neurocognitive impairment and imaging evidence of CNS calcifications and white matter loss. This raises the possibility that the long-term changes reported by Schuitema et al may not only be related to CRT; children treated for ALL on intensified chemotherapy protocols may be facing similar outcomes 25 years from now.

The report from Schuitema et al raises a number of concerns and opportunities. Some concerns regard the potential that survivors of current CNS and CNS-affecting therapies may face accelerated CNS aging, with the onset of dementia-like white-matter patterns occurring earlier than typically expected. Though this study does not make it possible to make individual predictions of severity of outcome, the level of disruption to the lives of individuals who might experience accelerated aging and the family members who take care of them can be extraordinary. For this reason, there should be a sense of urgency to learn more about the possibility of accelerated aging in the CNS-treated childhood cancer survivor population so that patients and their families can be fully informed and can access emerging treatments and initiate long-term planning, if necessary.

This article is but one report, and it does not signal the need for immediate discussions with patients and families that raise anxiety without offering only the possibility of accelerated CNS aging and no strategy for prevention or long-term treatment. It does, however, provide strong evidence to support initiation of studies of CNS and neurocognitive function of survivors of other types of cancer to determine whether the same patterns are observed. It provides a rationale for prospective studies of neurocognitive function of young survivors into adulthood to better understand the possible pattern of accelerated CNS aging. Information from these studies can be shared with survivors and their caregivers so long-term planning for care can be initiated. Further, there is an opportunity to examine individual (eg, genomic) and treatment-specific factors associated with accelerated aging. Are there polymorphisms or mutations that predict short-term neurocognitive impairment after treatment and are they associated with long-term late effects? Will we see the same patterns in children treated with high-dose methotrexate or other chemotherapy medications? These are but two questions that, if answered, might provide us with a way to modify therapy for children at high risk of CNS complications to change the late-effects risk without reducing survival rates. The childhood cancer scientific community has used knowledge of late effects outcomes to change primary therapy to reduce cardiac and neurocognitive late effects in the past, so this is not a new concept.

Although the challenges of providing treatment and support to the adult survivors and their families who experience long-term problems associated with long-ago therapy are daunting, there is an opportunity to embark on studies that may bring about changes in treatment and long-term outcomes for the children we are treating today. The potential impact of this late effect in terms of both financial cost and burden to the patient and family is great; a similarly great response from the scientific and funding community is needed. Schuitema et al have issued a wake-up call. The scientific community should not hit the snooze button.

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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REFERENCES

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