Introduction

Central nervous system (CNS) prophylaxis has been an essential component of the treatment of childhood acute lymphoblastic leukemia (ALL) for several decades. Early prophylactic treatment of CNS minimal residual disease is intended to guard against the possibility that CNS blasts not eradicated by systemic therapy will reseed the bone marrow, leading to relapse of the disease.[1] For many years, the preferred approach to CNS prophylaxis has been cranial radiation therapy (CRT), currently given at an 18-Gy dose, combined with intra-thecal methotrexate. This strategy is highly effective in preventing CNS relapse.[2,3]

The potential for long-term neurotoxicity associated with such intensive treatment in developing children, however, is an ongoing concern; cognitive impairment and short stature are commonly observed. Children diagnosed with ALL and treated with modern protocols experience excellent survival rates. As the number of survivors grows, the prevalence of these developmental toxicities becomes more clinically relevant. Although efforts have been undertaken to develop alternative methods of CNS prophylaxis that do not involve irradiation (such as intrathecal methotrexate, often given in combination with other drugs), treatment that includes CRT remains the preferred approach for children with high-risk disease.[4]

Although it is generally assumed that late neurotoxic effects result from CNS prophylactic therapy, the experimental designs of leukemia protocols may or may not allow this hypothesis to be tested. Central nervous system prophylaxis occurs in the context of complex treatment protocols that include a variety of neurotoxic agents. Therefore, it is important to document the risk for various toxicities and to determine to what extent they can be reliably associated with specific treatment components.

In the context of a randomized trial, outcomes can be clearly evaluated, and alternative approaches to CNS prophylaxis can be examined. Such opportunities are rare, however. More often, different approaches to CNS therapy are evaluated by comparing children assigned to different risk groups or protocols[5-7] or even children with different diseases.[8,9] In these situations, variations in CNS treatment may be confounded by other aspects of the protocol or the disease, rendering evaluation less reliable.

Furthermore, components of CNS prophylaxis may interact synergistically with systemic therapy[5-10]; CNS prophylactic treatment is associated with different outcomes depending on the systemic therapy. Therefore, in the discussion that follows, the late effects of CNS prophylactic therapy will be discussed and, when possible, related to specific components of such therapy. It should be understood, however, that in most instances, the more conservative approach is to relate late effects to the therapeutic picture with the assumption that CNS prophylaxis plays a major role.

Types of Toxic Effects

Although the major focus of this discussion is long-term toxic effects, significant acute toxic effects can be associated with CNS prophylaxis (Table 1).[1] Cranial irradiation has been associated with vomiting, anorexia, headache, and somnolence. Intrathecal methotrexate may be associated with acute arachnoiditis, pain at the site of the lumbar puncture, nausea and vomiting, fever, and an increase in intracranial pressure. Most of these acute toxic effects are short-lived, and few result in long-term consequences. Myelopathy and encephalopathy may also occur but are rare. The late toxic effects with the highest prevalence affect physical and mental development (Table 1). These effects are permanent, rather than acute, with the potential for causing lifelong problems. The
risk for a second malignancy is also increased in children treated with CRT, but the frequency is low.\[11\]

There are no good epidemiologic estimates on the prevalence of problems with cognitive development and physical growth, for several reasons: First, as will be discussed in detail below, the incidence and severity of these problems are highly dependent on a variety of factors, such as the specific characteristics of the leukemia treatment protocol and the age and gender of the child at the time of diagnosis. Prevalence, therefore, varies from institution to institution, depending on the treatment protocol used and the demographic characteristics of the children treated. Second, as will also be discussed below, with respect to cognitive issues, there is no standard way of defining outcome. Indeed, the definition of a learning disability, as a diagnosis, remains the subject of some controversy. Consequently, it is difficult to specify the prevalence of a "disorder." Risk for a particular child, therefore, is best estimated by consideration of the various factors discussed below. Ocular morbidity, attributed largely to corticosteroids, consists of posterior subcapsular cataracts. They tend to be asymptomatic and do not usually progress or cause loss of vision.\[12\] Dental complications are minimal with the low CRT dose (18 Gy), but preventive dental programs are important.\[13\]

The cognitive sequelae of therapy have been of greatest concern, and this issue remains a controversial topic. On the one hand, it is undesirable to employ a therapy that is known to cause lifelong impairment when such therapy is not necessary to achieve the desired medical outcome. On the other hand, effective therapy should not be withheld if it does not, in fact, cause such sequelae or if the medical outcome will be compromised. Moreover, the same therapy may be toxic in one group of patients but not in another. In such a situation, it would be unwise to deny the benefit of such therapy to the group who would not have experienced adverse effects to spare the group who would have been affected. Because of the confusion surrounding cognitive outcomes, the bulk of the discussion here focuses on these effects.

**Impact of Therapy on Physical Growth**

Children treated for ALL are at risk for a decrement in final adult height, often on the order of one standard deviation from expectation. Acute changes in growth rate are common during treatment, but recovery often occurs after cessation of treatment.\[14\] Of greater concern is the decreased amplitude of peak height velocity, a long-term effect that may occur during the adolescent growth spurt and is associated with a decrement in final height. Some studies have indicated that girls are more vulnerable to growth delay than boys. Menarche, as well as peak height velocity, may occur earlier in girls who have undergone treatment than in girls who have not.\[15\] Young age at treatment (before the age of 7) is a particular risk factor for girls,\[16,17\] with boys appearing to be far less vulnerable. In general, treatment protocols that include CRT are associated with a permanent decrease in height, whereas those that do not include CRT are not \[14,16,18\]. The specificity of the impact of cranial irradiation on growth is substantiated by preclinical studies.\[19\] Rats exposed to CRT, either alone or in combination with antileukemic drugs (eg, prednisolone, methotrexate), show disturbances in bone growth, whereas those exposed to drugs without CRT show no such disturbances. Clinically, children treated with a high dose of cranial irradiation (24 Gy) show more significant decrements in height than do those treated with a low dose (18 Gy),\[20\] but growth can be adversely affected by both doses. Children receiving lengthy, intensive maintenance drug therapy, however, may be at greater risk for diminished height.\[10\]

**Impact of Therapy on Mental Development**

**General Considerations**

Whereas the relationship between treatment and outcome is reasonably straightforward in the case of physical growth, it is more controversial with respect to mental development. A fundamental question centers on the end point to be measured. For height, the end point is clear, easily agreed upon, and reliably defined; however, this is not the case for mental development. There is no widely accepted technique for measuring cognitive outcomes, with the possible exception of the IQ test. The IQ test is a good indicator of a child's general level of cognitive functioning, and most investigators use it, which permits good comparability among studies. However, the IQ test is not sensitive to the subtler aspects of information processing that can manifest themselves in problems related to learning and social skills. Indeed, the hallmark of the definition of a child with a learning disability is that the child functions in the normal range of
intelligence but experiences unexplained difficulties at school. The IQ test is sensitive to neurotoxicity in severely affected children but can be insensitive to more subtle deficits, even though they may have a substantive functional impact. Consequently, investigators, particularly neuropsychologists, typically supplement the IQ test with other measures of information processing, although there is no standard way of doing so. Thus, outcome measures vary widely from study to study, depending on the theoretical bent or clinical practices of the investigator. This makes comparison of study results quite difficult.

**Role of CRT**

Probably the central questions throughout the literature on late cognitive sequelae are whether CRT affects outcome and, if so, to what extent. Of all the agents used in the treatment of leukemia, CRT has stimulated the most concern; the assumption is that observed cognitive deficits are primarily referable to CRT. A number of studies have indicated that children treated with cranial irradiation fare worse than a comparison group not given such treatment.[21-25] The majority of these studies evaluated cognitive outcomes in children treated with 24 Gy of CRT, a dose that is no longer commonly used. Because contemporary treatment protocols employ an 18-Gy dose of CRT, data that evaluate the impact of that dose are more relevant. In general, the trend is toward less severe toxic effects for protocols that involve the lower dose.[26] Several studies comparing groups treated with and without CRT at the 18-Gy dose document no differences in IQ or other measures.[5,27] Another multicenter study, however, did observe lower IQ scores in children treated with the 18-Gy dose than in those not treated with CRT.[7] The adverse impact of CRT, however, emerged only in the youngest children (less than 3 years of age at treatment), suggesting that for older children, CRT at the lower dose poses less risk.

Concurrent methotrexate therapy may affect the degree of toxicity associated with CRT.[5] Whereas an 18-Gy dose of cranial irradiation resulted in no discernible decrease in IQ scores, the same dose preceded by a single high dose (4 g/m²) of methotrexate resulted in a reliable decrement. Significantly, the same high dose of methotrexate did not result in adverse cognitive sequelae when treatment did not include CRT. Again, comparable findings have emerged from an animal model. Whereas CRT or methotrexate alone did not induce behavioral changes in animals, the combination of the two agents was associated with significant behavioral changes.[28]

Furthermore, adverse cognitive sequelae have been observed in children who did not receive CRT. In general, these sequelae do not entail IQ deficits, but rather, problems involving more specific skills. For example, comparable deficits in rote memory have been found in children treated with or without CRT.[26] Giralt and colleagues[29] compared children treated with CRT (24-Gy dose) and intrathecal methotrexate or intrathecal cytarabine and intrathecal methotrexate in the context of a randomized trial design. Both groups showed deficits relative to those of controls, but the magnitude of the deficits was similar in the two groups. Kaufmann and associates[30] describe declines in attentional, visual-motor, and academic skills in children for whom triple intrathecal therapy (methotrexate, cytarabine, and hydrocortisone) was used for CNS prophylaxis. In none of these studies, however, was it possible to determine to what extent any adverse outcomes were attributable to CNS prophylaxis per se and to what extent they reflected the impact of other components of treatment.

**Effects Related to Gender and Age**

As previously indicated, girls are more vulnerable than boys to growth changes associated with CRT. Heightened cognitive vulnerability in girls has also been observed; this vulnerability has emerged clearly in treatment protocols that included a high dose of cranial irradiation (24 Gy).[34-36] The basis for this phenomenon is unclear. Heightened vulnerability to toxicity in girls is not confined to the CNS; girls are also more vulnerable to anthracycline-induced cardiac toxicity.[37] Moreover, gender differences in treatment efficacy have been observed in some circumstances, with the rate of CNS relapse higher for boys than for girls.[38]

Gender-related differences are less evident, however, with a low dose of CRT (18 Gy).[26] At this lower dose, boys and girls appear to have essentially comparable cognitive outcomes. As previously
indicated, the impact of cranial irradiation can be exacerbated (for girls) by a high dose of methotrexate, a synergistic interaction that has not been observed in boys.[5]

Age-related effects have also been observed, with younger children more severely affected than older children.[7,34,36,39] Again, this effect is more prominent in girls.[34,36,39]

**Clinical Presentation of Neurobehavioral Problems**

As previously indicated, contemporary leukemia protocols are likely to result in subtle problems, rather than in global depression of IQ, as was seen following earlier, more intensive protocols. This is not to say that such problems will not have important consequences for a child’s daily functioning, but rather, that they are probably less severe than those seen a decade ago, when a 24-Gy dose of CRT was the normative dose. It is important to appreciate the qualitative nature of these problems, the way in which they manifest themselves in children’s lives, and their developmental course.

In the general population, the most commonly diagnosed learning disability syndromes are reading disability (dyslexia) and disordered attention (attention deficit hyperactivity disorder [ADHD]). These problems are relatively specific, tend to be idiopathic, and often seem to run in families. The problems seen in children who have undergone treatment of ALL, however, tend to be of a different nature. Learning problems seen in these children often involve so-called nonverbal learning disabilities.[40] Most of these children acquire elementary reading skills without too much difficulty, although some may require support, and few exhibit the impulsivity, overactivity, and distractibility characteristic of ADHD. Although many children exhibit apparent attentional problems, they are best understood as being secondary to cognitive issues, as described in greater detail below, rather than as being a primary attentional syndrome or ADHD.

Metacognitive problems have been described in survivors of leukemia in a variety of contexts than can involve working with complex material that is either verbal or nonverbal.[41-43] The term "metacognition" means "knowing about knowing," that is, developing strategies for solving problems and understanding the nature and organization of knowledge. Metacognition implies knowledge and insight into one’s own thought and problem-solving processes. Children with metacognitive problems can approach new material in a relatively concrete fashion, becoming overly involved with superficial aspects without moving on to the more conceptual level. Exhibiting inferential reasoning and making connections from prior knowledge to new material can be difficult.

Another common problem involves rote memory and retrieval of factual information.[27] Children with this problem may experience greater-than-expected difficulty in remembering names and facts in social studies and science classes. In mathematics, retrieval of number facts may lack fluency, thus compromising speed, efficiency, and accuracy of numeric computation. Spelling is a related area of vulnerability.[5]

The metacognitive nature of these problems has clinical implications. First, these children’s difficulties will not necessarily manifest as a deficit in a discrete skill area, and therefore, their formal scores on psychometric testing may not deviate substantially from those expected for children their age. Nevertheless, parents may report that their children are struggling academically because they work inefficiently, reverting to a deliberate, step-by-step approach to compensate. School personnel may not be sure that there is a problem because test scores can be relatively normal. This can be a source of friction as families struggle to support children who are experiencing unexplained school-related stress.

Second, problems may appear inconsistently. Because the primary issue involves how children approach a task, or their level of efficiency, there is no specific reference symptom; rather, there is a general sense of struggle. Children with these problems may be able to learn a mathematics topic well enough to pass a test or complete a homework assignment, and yet when the same material is presented in another context or several months later, they may appear bewildered. This can be puzzling to parents and teachers, often raising questions of motivation. The inconsistency may be interpreted as attentional, and ADHD may be suspected. The apparent inattention or inconsistency, however, may be secondary to cognitive overload or confusion.

Third, children with these problems often exhibit a characteristic developmental course. In essence, they may be successful in the early grades but may begin to falter in the upper elementary grades and middle-school grades. This does not usually represent a progressive deterioration of function as a consequence of therapy, although neuropathologic changes may occur for some years after the completion of therapy.[44] Instead, the demands and expectations of the upper grades demand greater efficiency, an ability to digest larger volumes of material and infer concepts, and an ability to work independently. It is with regard to such expectations that children treated for ALL can be most vulnerable. Thus, they may appear to develop problems when, in fact, the problems were always present but the challenges were not yet sufficient to elicit them.
Finally, the same cognitive issues that affect academic performance may also manifest in the development of social skills, particularly as children approach adolescence.[45,46] With development, social interaction involves processing information from multiple sources, making inferences about intention that may not be supported by the literal meaning of language, and grasping subtle cues embedded in the social context. All of these tasks can be difficult for some children, and problems may be manifested by occasional withdrawal or isolation, initially more as a function of bewilderment than of depression. This may occur at the same age at which differences in linear growth become most apparent, and this constellation can be particularly troublesome.

**Interventions**

Routine follow-up of children for the sequelae of CNS prophylaxis of ALL should include regular dental visits, as well as occasional ophthalmologic visits. If growth problems occur, an endocrine evaluation may be warranted. The commitment to long-term follow-up is essential so that problems can be treated early, averting more significant consequences. This is probably most important in the area of learning.

Any child treated on a leukemia protocol is a priori at risk for learning problems. Although these problems may not necessarily assume the form of specific difficulties with reading, calculation, or attention, children nevertheless may experience legitimate struggles in and out of school that should be acknowledged. Depending on the treatment protocol, girls may be more vulnerable than boys; children treated with radiotherapy may be more vulnerable than those who do not receive such therapy; and children treated at young ages may be more vulnerable than children treated at older ages. As previously suggested, however, the fact that children were treated without cranial irradiation does not mean that there will be no associated learning problems, and these children require equal vigilance. The late elementary and middle-school years can be particularly challenging, and therefore, children who have been reasonably successful in the early years should still be followed carefully during this developmental period.

Any early indication of academic or social struggle should be taken seriously and a professional evaluation undertaken. Children who achieve scores in the normal range on formal testing can nevertheless experience legitimate difficulty in complying with grade-level demands. Hospital-based pediatric psychologists or neuropsychologists, who have more extensive experience with these children than community-based practitioners, often are more alert to problems that were not evident on standardized testing. In any event, the first step is to identify the problem and confirm that the struggle is legitimate, not primarily indicative of poor motivation, ADHD, or emotional concerns (although they may be present as well).

Management of learning difficulties can focus on providing support in metacognitive development. This approach can involve not only teaching children organizational strategies but also offering ways to help them gain an appreciation of organizing concepts and frameworks. Children can benefit from learning environments that provide a high degree of structure with underlying concepts and frameworks made highly explicit. They often need extra reinforcement of concepts, as well as direct support in making connections from concepts to specifics, and vice versa. Modest interventions of this type may often result in dramatic improvements.[43]

If present, problems with rote memory should be acknowledged as well. Technological support can be of considerable help. Some children, for example, benefit from a calculator in class so that they can devote their attention to the reasoning aspects of problem-solving and calculation tasks. Children with problems in spelling and writing can be taught writing strategies as well as shown how to use the "spell-checker" in a word processor or a hand-held spelling device. Again, identifying and acknowledging the problem as legitimate can allow solutions to emerge.

Finally, interventions should be sensitive to the social context and address the whole child.[47] As indicated, some children may experience social difficulties that are essentially cognitively based.[40] If so, the intervention should be cognitive as well, helping the child develop strategies for dealing with social situations. In other instances, social difficulties may stem more from emotional problems, and thus, traditional psychotherapy may be more effective than other approaches. Again, this distinction can be made on the basis of a professional evaluation.

**Summary**

Contemporary protocols for treating ALL in children have been remarkably successful in achieving high rates of survival. Along with this success has come a burden of late developmental problems involving linear growth and cognitive development. Although the more recent treatment protocols...
are associated with less severe toxicity than past protocols, the problems experienced by these children nonetheless demand attention. Cranial irradiation may be associated with an increased risk for problems, especially among children treated at a young age (less than 3 years) and girls who also receive high-dose methotrexate. Children treated without CRT may exhibit late effects as well, although more so in cognitive development than in growth. Late-middle childhood and early adolescence can be periods of particular vulnerability, because the toxic effects of CNS prophylaxis on cognitive, social, and physical development become more apparent during these times. Medical management demands a commitment to long-term follow-up. Educational management should focus first on assessing the problems of children and legitimizing their complaints and then on providing supports that can render their world more comprehensible and manageable. These children can be quite responsive to such interventions, and the outlook is quite positive.

**References:**


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