10. LONG TERM COMPLICATIONS OF THERAPY

The treatment of children and adolescents with the common malignant solid tumors has become increasingly successful. With the prolonged survival of these patients, complications related to the therapy which was received have been identified. Some complications appear at the present time to be unavoidable if long-term survival is to be achieved. Other complications, however, may be avoidable in certain groups of patients. Increasingly, pediatric oncologists must determine whether the risk of a certain therapy, in terms of acute and long-term toxicity, is offset by an equivalent or greater benefit as measured by long-term, relapse-free survival.

Central Nervous System

The use of combined modality therapy to prevent or treat the spread of a malignancy to the central nervous system (CNS) is associated with the occurrence of functional and pathological changes which can be associated with significant morbidity. Subacute leukoencephalopathy was described in 1974 by Price and Jamieson 327. Pathologically, this lesion was characterized by diffuse, reactive astrocytosis and multiple, non-inflammatory necrotic foci which frequently contained mineralized cellular debris. The presence of this lesion was associated with the administration of intravenous (IV) methotrexate (MTX) following CNS irradiation with a dose of 2000 rads or more, and the occurrence of one or more episodes of CNS leukemia 327. Subsequently, Price and Birdwell described the presence of mineralizing microangiopathy and dystrophic calcification in the CNS of children who had died of acute lymphoblastic leukemia (ALL). This lesion always involved the lenticular nucleus, and was identified in the cortex of 35.7% (10/28) of the patients with involvement of the lenticular nucleus 326. The lesion occurred in patients who survived for more than ten months after completing CNS irradiation, and who had two or more episodes of CNS leukemia. Others reported varying degrees of cerebral atrophy in 67.6% (46/68) of patients with ALL. The frequency of moderate or severe atrophy was 42.8% (6/14) in patients treated with intrathecal (IT) MTX compared to 45.8% (11/24) in patients treated with IT MTX and cranial irradiation 89.

Peylan-Ramu et al reported abnormalities in computerized tomographic (CT) scans of the head in 53.1% (17/32) of patients who received prophylactic CNS therapy with cranial irradiation and IT chemotherapy. The frequency of abnormal scans was the same among patients who received IT MTX (57.1%, 8/14) and those who received IT cytosine arabinoside (50%, 9/18). IT therapy was given to these patients monthly for 30 months. The abnormalities identified included ventricular dilatation, subarachnoid space dilatation, decreased attenuation coefficient and intracerebral calcification 312.

Several subsequent studies reported lower frequencies of CT scan abnormalities in patients following various programs of CNS prophylaxis. Day et al reported normal CT scans in 100% (27/27) of children following cranial irradiation and IT MTX. Most children received five doses of IT MTX (12.5 mg/m²) during cranial irradiation 100. Kolmannskog et al reported CT scan abnormalities in 5.3% (1/19) of patients who received CNS prophylaxis with IT and high-dose, IV MTX 206. Ochs et al reported abnormal CT scans in 18.6% (8/43) of patients treated with IT and high-dose IV MTX.
for CNS prophylaxis. The patients in these three series did not receive maintenance IT chemotherapy, whereas the patients reported by Peylan-Ramu all received prolonged maintenance IT chemotherapy.

The interpretation of these studies was difficult because few studies documented the frequency of abnormal CT scans in patients with ALL prior to any CNS therapy. Three studies have reported this frequency as 15.4% (2/13), 18.2% (2/11) and 31.2% (10/32).

Recent studies have suggested that the frequency of CT scan abnormalities was similar following CNS prophylaxis with IT MTX or cranial irradiation and IT MTX. Esseltine et al reported abnormal CT scans in 42.8% (6/14) of patients who received cranial irradiation and IT MTX, compared to 25% (3/12) of patients treated with only IT MTX. This difference was not statistically significant. Ochs et al reported CT scan abnormalities in 9.1% (5/55) of prospectively evaluated patients who received CNS prophylaxis with cranial irradiation and IT MTX, compared to 19.2% (10/52) of patients who received high-dose IV and IT MTX for CNS prophylaxis.

Prophylactic CNS therapy has been recommended for some patients with embryonal rhabdomyosarcoma and Ewing's sarcoma. Bode et al reported that no CT scan abnormalities were identified in 15 patients who received cranial irradiation (2000 rads) and IT MTX for the prevention of CNS recurrence of Ewing's sarcoma. No CT scan abnormalities were identified in 18 patients who received combination chemotherapy which included high-dose (2.5 - 5.0 grams/m²) MTX for the adjuvant treatment of osteosarcoma.

The studies of CT scan abnormalities in children with ALL demonstrated the difficulty of attributing significance to an abnormal finding on one scan, without considering the frequency of such abnormalities in patients prior to treatment, and the role of various treatment programs in the genesis of the abnormalities identified.

Soni et al examined the neuropsychological effects of prophylactic CNS treatment. Employing two intelligence tests, the Stanford-Binet Intelligence Scale and the Wechsler Intelligence Scale for children, these investigators identified no adverse effects of prophylactic cranial irradiation and IT MTX on intellectual function.

Eiser evaluated 28 children with ALL employing the Wechsler Intelligence Scale for Children and the Burt Reading Test. She identified significant differences in full scale, verbal and performance IQ when children who received early CNS prophylaxis with cranial irradiation were compared to those who received such therapy 6 or more months after diagnosis, or those who received no CNS irradiation. Subsequently, Eiser reported that the mean full scale IQ of 40 children treated for ALL using protocols which included prophylactic cranial irradiation (2400 rads) was 93.83, compared to 105.75 for controls. This difference was highly significant. The mean IQ of 16 children treated for various solid tumors was 101.37, compared to 106.50 for control children. This difference was not statistically significant.

McIntosh et al evaluated 23 children with ALL who remained in continuous remission for one or more years. All had received prophylactic cranial irradiation. Eleven children had no evidence of motor abnormalities, seizures or learning disability. These children received biweekly maintenance therapy which included IV MTX, with a mean dose of 217 mg/m² (range 114 - 315 mg/m²). Twelve children had neurological symptoms, including five with seizure disorders and three with learning disabilities. These children received biweekly IV MTX, the mean dosage being 240 mg/m² (range 167-448 mg/m²).