Neurologic Complications of Chemotherapy

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Leukemia, brain tumors (glioma, medulloblastoma), and neuroblastoma constitute the most common types of childhood cancers. Each year in the United States, approximately 3000 children, on average, receive a diagnosis of leukemia, making it the most likely cancer to be encountered in pediatric practice.

Advanced chemotherapy and treatment regimens have made longer survival the norm for most forms of childhood cancer, with 5-year survival rates as high as 80%. Unfortunately, life-threatening or permanently disabling treatment-related adverse events are known to occur in 40% of these childhood survivors. Such data make clear how important it is for the pediatrician to be able to identify adverse events related to commonly used chemotherapies and take appropriate action.

This discussion will focus on the neurologic complications of medications used in the treatment of leukemia, lymphoma, and certain other solid tumors of childhood. Specific treatment options may not exist in all cases. Nonetheless, they are mentioned in the relevant areas.

Peripheral Nervous System

Paresthesias often herald the onset of peripheral neuropathy. Pain may follow. Other symptoms that may occur are ataxia and motor weakness, especially in the form of foot drop or wrist drop. Cranial nerves can be involved and manifest as diplopia related to extraocular muscle palsy; dysphonia as a result of vocal cord paralysis, or sensory neural hearing loss. In children, even a mild degree of hearing loss may affect language acquisition, day-to-day social interaction, and processing of the spoken word. Autonomic neuropathy may lead to constipation, paralytic ileus, urinary retention, or orthostatic hypotension.

The chemotherapeutic agents most widely implicated in peripheral neuropathy are vincristine, cisplatin, paclitaxel, and carboplatin. Gabapentin or pregabalin can help alleviate the associated discomfort. Certain medications, such as vincristine, are thought to cause peripheral neuropathy in a dose-dependent manner. Dosage modification may ameliorate disabling symptoms.

Certain drug combinations, such as methotrexate and intrathecal cytarabine, can lead to specific localized neuropathy such as the cauda equina syndrome. Urinary and fecal incontinence are prominent features of the syndrome, sometimes in association with lower back pain. Urinary incontinence is frequently missed in a child who may have been recently toilet trained.

Central Nervous System

Brain

White matter damage, ie, leukoencephalopathy, is a recognized adverse effect of certain medications used to treat leukemia, most notably methotrexate. The highest incidence of this type of damage is seen among preschool-aged children. Consciousness level may be altered, causing confusion, disorientation, hallucinations, or lethargy. Other symptoms that may occur in the acute stage of leukoencephalopathy include convulsions, headache, vision loss, hemiparesis, and aphasia. Subacute onset of dementia may be seen, with intellectual deterioration and school difficulties. White matter damage is a particular risk when intrathecal methotrexate is combined with cranial radiation. Withholding methotrexate for a short period may help hasten recovery. In rare instances, disseminated coagulation necrosis may occur, which carries a more serious prognosis.
Several chemotherapeutic medications, including L-asparaginase, cytarabine, cisplatin, cyclophosphamide, and intravenous methotrexate can lead to reversible posterior leukoencephalopathy (previously referred to as PRES [posterior reversible encephalopathy syndrome]), wherein bilateral parietal and occipital lobes are involved by diffuse cellular edema. Seizures and visual loss are presenting symptoms of reversible posterior leukoencephalopathy. As the name implies, it tends to be transient and non-progressive, with resolution of clinical and radiological features over time.

Treatment with L-asparaginase can lead to vascular complications, including hemorrhagic or ischemic stroke that often may involve venous sinuses. Vascular events tend to occur after the first 14 days of treatment. Presenting symptoms are headache; seizures; altered level of consciousness; diplopia due to cranial nerve palsies; vomiting; and focal deficits, such as vision loss or motor weakness.

Cerebellar degeneration is associated with several chemotherapeutic agents. Clinically, cerebellar involvement manifests as ataxia, head nodding (titubation), tremor of the outstretched hand, nystagmus, and dysarthria. Cytarabine and 5-flourouracil are well known to cause cerebellar damage. A mild reversible type is more common in childhood, compared with that seen in adults over the age of 50 years, who tend to experience severe Purkinje cell damage.

Aseptic meningitis, a known complication of intrathecal medications such as methotrexate, can present with headache, stiff neck, fever, and vomiting.

**Spinal Cord**

Intrathecal administration of medications is now standard of care for CNS prophylaxis in children with acute lymphocytic leukemia. It is highly effective in reducing CNS relapses. This administration route, however, carries its own risks, including chemical arachnoiditis (irritation of the meninges), ascending myelitis, and myelopathy. The myelopathy is associated with significant morbidity and mortality, with most series reporting few cases of complete recovery. This catastrophic complication has been noted most commonly following a regimen that combines intrathecal methotrexate and cytarabine. MRI shows cord edema with gadolinium enhancement and may subsequently reveal cord atrophy. Important physical findings include motor weakness, a clearly defined level below which sensation is impaired; sphincter incontinence; and in the acute stage, absent reflexes. Use of corticosteroids in this situation may not be of much benefit.

In conclusion, chemotherapy in young children may be associated with significant neurologic toxicity—both acute and long-term. Familiarity with these conditions will enable pediatricians to continue to be valuable resources for families as they navigate the difficult path of childhood cancer.

**References**


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