Neurologic Complications of Systemic Anticancer Therapy

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KEYWORDS

• Neurologic complications • Neurotoxicity • Chemotherapy • Targeted agents
• Immunotherapy

KEY POINTS

- Neurologic complications of systemic cancer therapy represent an increasing problem for practitioners, as survival of cancer patients is improving, and new therapeutic agents are being developed.
- It is important to differentiate treatment-related neurologic complications from disease recurrence in the nervous system and paraneoplastic disease.
- Although neurologic complications are relatively rare with newer agents such as monoclonal antibodies and immunotherapy, their presence can be associated with significant morbidity and/or mortality.

INTRODUCTION

Neurologic complications secondary to cancer treatment-related toxicity arise either as a result of direct toxic effects on the nervous system or as an indirect consequence of treatment-induced metabolic, vascular, autoimmune, or infectious abnormalities. Symptoms can range from mild and transient to severe and permanent. When permanent, symptoms can be greatly debilitating to patients and compromise their quality of life. Both neurologists and neuro-oncologists are likely to encounter an increase in the number of patients with treatment-induced neurotoxic complications in their practice, given the increasing number of cancer survivors in the era of novel therapeutics, including targeted agents and immunotherapy. Differentiation between treatment-related toxicity, disease recurrence in the form of nervous system metastases, and paraneoplastic phenomena is important to guide appropriate management. This article focuses on the chemotherapy agents most likely to cause neurologic complications

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(Table 1), as well as novel targeted and immunotherapeutic agents that have transformed the landscape of cancer treatment in recent years (Table 2).

Cytotoxic Chemotherapy Agents

Antimetabolites

Methotrexate Methotrexate (MTX) is a dihydrofolate reductase inhibitor that reduces the amount of tetrahydrofolate available for DNA synthesis, which eventually leads to cell death.[1] It is used in the treatment of leukemia, primary and secondary central nervous system (CNS) lymphoma, choriocarcinoma, and osteosarcoma. In addition, it is frequently administered via the intrathecal (IT) route for leptomeningeal metastases. Given its effect on folate metabolism, MTX is typically administered with leucovorin to prevent folate depletion in noncancerous cells. MTX can cause a wide range of acute, subacute, and chronic neurologic complications.

Aseptic meningitis occurs most commonly in the setting of IT MTX administration and affects approximately 10% to 30% of patients,[2,3] although incidence rates as high as 61% have been reported.[4] Symptoms are indistinguishable from those of other noninfectious and infectious causes of meningitis and include headache, nuchal rigidity, back pain, nausea, vomiting, fever, and lethargy. Symptoms typically start 2 to 4 hours after administration and can persist for 2 to 6 days.[4,5] Interestingly, the inflammatory response may be attenuated in the setting of concomitant brain irradiation.[4]

IT MTX can also lead to a transverse myelopathy; the cumulative incidence is approximately 3% for IT MTX and cytarabine (Ara-C), which are the most frequently administered drugs via the IT route.[6] Patients typically experience lower extremity sensory loss, paraplegia, and, to a variable degree, sphincter dysfunction.[6–8] Time to onset of neurologic symptoms can be highly variable, ranging from 2 days to 7 months after starting IT chemotherapy.[6,7] The occurrence of symptoms is not dose-dependent, suggesting that individual patient factors may predispose to the myelopathy.[7] Notably, spine MRI can reveal abnormal T2 hyperintensity of the dorsal column in some cases,[7] although a normal MRI should not exclude the diagnosis of transverse myelopathy. Improvement of symptoms is variable after administration of steroids, intravenous immunoglobulin, or radiation therapy.[6,7]

Both acute and subacute encephalopathy syndromes have been observed after high-dose intravenous and IT MTX.[9–11] Symptoms include confusion, disorientation, seizures, and focal neurologic deficits and usually emerge 5 to 13 days after drug administration. Brain MRI is characteristically normal.[9] In most cases, these deficits resolve spontaneously within 1 to 3 days, and patients are able to receive further courses of MTX without modifications in dose or route of administration.[9] It has been proposed that downstream methionine depletion and accumulation of homocysteine via inhibition of dihydrofolate reductase contribute to the pathogenesis of MTX encephalopathy.[1,12] Genome-wide association studies in childhood ALL patients have not revealed any definitive genetic markers that predict the likelihood of neurotoxicity.[13]

A debilitating chronic neurotoxic effect of intravenous and IT MTX is leukoencephalopathy, which begins months to years after completion of treatment. Characteristic features include progressive cognitive dysfunction, ranging from mild cognitive impairment to severe dementia, somnolence, seizures, ataxia, and hemiparesis.[14] The effects of MTX-induced white matter damage are potentiated by concurrent brain irradiation and related to the cumulative dose of MTX.[14,15] Brain MRI typically demonstrates cerebral atrophy and T2/FLAIR-hyperintense changes affecting the white matter (Fig. 1).