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Nitrosoureas Toxicity

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Continuing Education Activity

Nitrosourea toxicity is a potentially serious complication of alkylating agents used to treat high-grade gliomas, glioblastomas, and selected hematologic and solid malignancies. The agents' high lipophilicity facilitates blood-brain barrier penetration but contributes to dose-dependent toxicities, including myelosuppression, pulmonary fibrosis, hepatotoxicity, nephrotoxicity, and neurologic injury. Clinical manifestations vary by affected organ and may include cytopenias, respiratory symptoms, hepatic or renal dysfunction, and neurologic deficits. Diagnosis relies on clinical assessment, laboratory testing, and organ-specific imaging. No specific antidote exists. Management consists of treatment discontinuation, supportive care, and close monitoring to limit morbidity. This activity for healthcare professionals is designed to sharpen learners' skills in evaluating and managing nitrosourea toxicity. Participants strengthen their understanding of relevant toxicokinetics, clinical manifestations, and evidence-based diagnostic and treatment recommendations. Enhanced competence empowers clinicians to recognize treatment-related toxicities, implement supportive care, and collaborate with interprofessional teams to optimize patient safety and outcomes.

Objectives:

- Differentiate between symptoms of malignancy and toxicity from nitrosourea chemotherapy based on the timing of symptoms relative to chemotherapy, organ-specific manifestations, and diagnostic findings.
- Identify features of nitrosourea toxicity that indicate a high risk of life-threatening complications and require intervention.
- Implement patient-specific, evidence-based approaches for managing nitrosourea toxicity and mitigating its potential complications.
- Collaborate with all members of the interprofessional team, including specialists such as emergency medicine and critical care clinicians as well as medical toxicologists, to provide efficient, comprehensive, and coordinated care for individuals experiencing nitrosourea toxicity.

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Introduction

Nitrosoureas are cytotoxic chemotherapeutic drugs that kill cells by damaging DNA. Clinicians use nitrosoureas to treat malignancies, including malignant glioblastomas, Hodgkin and non-Hodgkin lymphomas, and pancreatic islet cell tumors. Three of the most commonly used nitrosourea compounds are 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU, also known as carmustine), 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU, also known as lomustine), and fotemustine.[1] Nitrosoureas are lipophilic compounds with antitumor and cytotoxic effects mediated through alkylation and carbamoylation and remain active across multiple phases of the cell cycle.

Lomustine readily crosses the blood-brain barrier and is commonly used for recurrent glioblastoma multiforme. Some European countries use fotemustine in place of lomustine. Carmustine was the first nitrosourea developed for public use and received United States Food and Drug Administration approval in 1977. Carmustine use has declined because of toxicity, intravenous administration, and limited availability.[2]

Nitrosoureas may be administered as part of combination chemotherapy, such as the procarbazine, lomustine, and vincristine (PCV) regimen used to treat oligodendroglioma, or as standalone agents.[3] Streptozocin has methyl nitrosourea activity against pancreatic islet cell tumors.[4] Nitrosoureas are associated with significant adverse effects, including leukoencephalopathy, pulmonary toxicity, nephrotoxicity, hepatotoxicity, neurotoxicity, myelosuppression, secondary leukemias, nausea, vomiting, stomatitis, alopecia, anemia, anorexia, and phlebitis and burning at the injection site.[5][6] Given the severe adverse-effect profile, nitrosoureas are mostly used for tumor recurrence or refractory cases.[7] Nitrosourea metabolites are primarily excreted through the kidneys.

Etiology

Nitrosoureas are a class of chemotherapeutic drugs containing a nitroso group and a urea group. Nitrosoureas are most often used to treat high-grade gliomas, recurrent glioblastoma multiforme, pulmonary cancers, and pancreatic islet cell tumors. These agents are also an important component of the BEAM (BCNU, etoposide, cytarabine, melphalan) conditioning regimen for autologous hematopoietic stem cell transplantation in lymphoma.[8] Severe, dose-dependent adverse effects limit nitrosourea use as first-line therapy.

Epidemiology

High-grade gliomas account for approximately 80% of intracranial malignant tumors and are the most common primary intracranial malignancy. High-grade gliomas have a poor prognosis, with a median overall survival of less than 2 years. Glioblastomas account for 49.1% of primary central nervous system tumors, with a 5-year survival rate of 6.8%.[9] The frequency of adverse effects from nitrosourea therapy varies according to patient factors and the targeted malignancy. Pulmonary fibrosis, which may be diffuse and severe, occurs in 10% to 30% of patients receiving carmustine therapy.[10]

Pathophysiology

Nitrosoureas produce reactive intermediates. A key intermediate, a chloroethyl carbonium ion, can create adducts and cross-link DNA strands. Isocyanate is also produced as an intermediate and alters DNA repair enzymes through carbamylation. Aqueous decomposition into these reactive intermediates leads to cellular damage and, ultimately, cell death.

Nitrosoureas are highly lipophilic and able to cross the blood-brain barrier, making them effective against central nervous system tumors. Nitrosourea toxicity can affect nearly every organ system. Patients with intrinsic or acquired high levels of O6-methylguanine-DNA methyltransferase are resistant to the cytotoxic effects of alkylating agents, which may render nitrosourea therapy ineffective.[11] Nausea and vomiting are the most common presenting symptoms of nitrosourea toxicity and can occur within a few hours after treatment initiation. Most other toxicities manifest weeks to months after initial exposure.

Neurotoxicity

The neurotoxic effects of nitrosourea compounds have led to their use in animal experiments to induce neurotoxicity and simulate Alzheimer disease. Streptozotocin causes memory impairment, decreased antioxidant capacity, and amyloid β plaque deposition.[12] The agents 1-

(4-amino-2-methylpyrimidin-5-yl)methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride (ACNU) and 1-(4-amino-2-methylpyrimidin-5-yl)methyl-3-(2-chloroethyl)-3-nitrosourea (MCNU, also known as ranimustine) have been associated with brain edema, headache, nuchal stiffness, vomiting, motor weakness, and cranial nerve palsies.

Pathologic changes include capsule formation, spongy degeneration, reactive gliosis of adjacent white matter, occlusion of neighboring arteries, and demyelination of cranial nerves. Focal brain necrosis has been reported in patients treated with MCNU.[13] BCNU pharmacovigilance data have identified associations with eosinophilic meningitis, pneumocephalus, and intracranial hypotension.[14]

Cardiotoxicity

Preclinical models suggest that carmustine may cause systolic dysfunction, with decreased ejection fraction and cardiac output and increased left ventricular internal dimension and end-systolic left ventricular volume on echocardiography. Definitive human data are lacking.[15]

Pulmonary Toxicity

Nitrosourea compounds cause dose-dependent pulmonary toxicity, which may manifest as pulmonary fibrosis, similar to other alkylating agents. Pulmonary fibrosis occurs in an estimated 10% to 30% of patients treated with carmustine. Initial presentation may include pulmonary edema and infiltrates, followed by progressive fibrosis. Irreversible and progressive pulmonary insufficiency may develop, leading to hypoxemia and death.[16]

Nephrotoxicity

Carmustine and semustine have demonstrated nephrotoxic effects in patients receiving therapy for malignant brain tumors. Nephrotoxicity appears to be dose-dependent and may cause impaired renal function, manifested by elevated blood urea nitrogen and serum creatinine levels or decreased filtration rates measured by inulin clearance. Renal injury may occur without preceding urinary abnormalities. Severe nephrotoxicity may cause uremia. Hepatic metabolism of nitrosoureas is hypothesized to produce a nephrotoxic metabolite that damages renal tissue. [17] Streptozotocin has also been shown to cause proximal tubular injury.[18]

Hepatotoxicity

Hepatotoxicity may occur in up to 26% of patients treated with nitrosourea analogs, causing reversible serum liver enzyme elevations, hepatomegaly, hepatocyte necrosis, and jaundice. Clinical manifestations of hepatotoxicity usually develop at least 2 weeks after treatment initiation and often resolve spontaneously. However, hepatocyte necrosis may persist for up to 4 months after exposure.[19]

Myelosuppression

Nitrosoureas cause delayed and cumulative bone marrow toxicity, with a nadir occurring approximately 4 to 6 weeks after administration.[20] The platelet nadir occurs about 27 days after drug administration, whereas the leukocyte count nadir occurs approximately 35 days after therapy.[21] High doses may cause permanent bone marrow damage. Study results have not demonstrated that lithium administration with nitrosoureas can counteract myelosuppression, unlike lithium administration for vinblastine toxicity.[22][23]

Histopathology

The histological features of pulmonary toxicity caused by nitrosoureas resemble those of pulmonary disease caused by other chemotherapeutic agents. Lung biopsy and autopsy findings reveal end-stage pulmonary disease characterized by edema, desquamation of alveolar type I

cells, hyperplasia and hypertrophy of alveolar type II cells, and diffuse interstitial fibrosis. Alveolar septa and bronchial and capillary walls demonstrate pronounced increases in collagen bundles, fibroblasts, and plasma cells.

Typical histological features include bronchiolar epithelial hyperplasia, early squamous metaplasia, and peribronchiolar granulomatous lesions. Renal biopsies from patients with nitrosourea toxicity demonstrate tubular atrophy, interstitial fibrosis, and glomerular sclerosis. [24] Hematoxylin and eosin staining of postmortem liver samples from patients who received nitrosourea therapy reveals bands of fibrosis with nodules of acute and subacute necrosis.

Toxicokinetics

Researchers have studied the pharmacological effects of lomustine at therapeutic doses. Following oral administration of lomustine at doses ranging from 30 mg/m² to 100 mg/m², approximately half of the administered dose is excreted in the urine as degradation products within 24 hours. The serum half-life of lomustine is approximately 90 minutes, whereas lomustine metabolites may have substantially longer half-lives.

History and Physical

Patients with high-grade malignant gliomas, glioblastoma multiforme, or metastatic cancers receiving nitrosourea chemotherapy are at high risk of nitrosourea toxicity. In patients with a family member currently undergoing nitrosourea chemotherapy, nitrosourea toxicity should be considered in the differential diagnosis after accidental or intentional ingestion. Patients may report nausea, vomiting, and diarrhea in the acute setting. Long-term complaints include dyspnea, dry cough, and fluid retention.

Physical examination findings may include petechial rash, fever, scleral icterus, and bleeding gums secondary to myelosuppression and hepatotoxicity. Pulmonary examination may reveal diffuse fine crackles, tachypnea, and dry cough. Gastrointestinal examination findings include guarding, jaundice, abdominal tenderness, and pain. Neurologic examination can be challenging without knowledge of the patient's baseline neurologic status because malignancy, radiation therapy, or tumor resection may cause preexisting neurologic deficits. Neurologic findings may include cranial nerve palsies, motor weakness, and cognitive slowing.

Evaluation

A complete blood count with differential is a key laboratory test for monitoring delayed myelosuppression. A metabolic panel should be obtained to assess for electrolyte abnormalities, uremia, or creatinine elevation associated with renal dysfunction, along with hepatic function tests, including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin, to assess for hepatotoxicity. Chest radiographs may demonstrate pulmonary infiltrates, whereas chest computed tomography may show honeycombing, traction bronchiectasis, lung architectural distortion, reticulation, and interlobular septal thickening.[25]

Abnormalities in the diffusing capacity for carbon monoxide may be the earliest indicator of pulmonary damage. Pulmonary function tests can track the severity of pulmonary tissue damage. Hydroxyproline levels can quantify pulmonary fibrosis, but the usefulness of hydroxyproline measurement in patients with nitrosourea-induced pulmonary fibrosis remains uncertain. Carmustine inhibits fatty acid synthesis in pulmonary alveolar type II cells in a dose-dependent manner, and the rate of fatty acid biosynthesis is a sensitive marker of carmustine-induced lung toxicity.

Treatment / Management

Treatment of nitrosourea toxicity consists of supportive care and discontinuation of the offending agent because no specific antidote or reversal agent has been identified. Patients with significant myelosuppression should be admitted to the hospital for platelet transfusion to maintain a platelet count above 10,000/mm³ and red blood cell transfusion to maintain a hemoglobin concentration above 7 g/dL. Hematologic parameters, including platelet counts, may require several weeks to recover after chemotherapy.

Erythropoiesis-stimulating agents (ESAs) can reduce transfusion requirements and are recommended for certain adults and children with chemotherapy-associated anemia.[26][27] ESAs may be offered to adults with hemoglobin concentrations below 10 g/dL when treatment intent is not curative.[28] Antibiotic and antifungal prophylaxis may be indicated for patients with profound and prolonged neutropenia.[29] Select antibiotics based on local epidemiology and susceptibility patterns.[30]

Patients with nephrotoxicity require clinical monitoring and adequate hydration. Correct protein and metabolic abnormalities to maximize renal protection.[31] Corticosteroids may treat nitrosourea-induced pulmonary fibrosis, but results from studies have not shown significant benefit from corticosteroid therapy during nitrosourea treatment.[32] Pulmonary fibrosis may progress after cessation of nitrosourea therapy.

Differential Diagnosis

The differential diagnosis of nitrosourea toxicity includes pulmonary, rheumatological, hepatological, hematological, nephrological, and neurological disorders that can produce similar clinical manifestations. Respiratory symptoms or pulmonary infiltrates warrant consideration of restrictive lung diseases, including pulmonary fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, and pneumonia. Systemic autoimmune conditions with overlapping pulmonary or systemic manifestations include dermatomyositis, polymyositis, mixed connective tissue disease, pneumoconiosis, systemic lupus erythematosus, rheumatoid arthritis, and scleroderma.

Hepatic dysfunction or jaundice may result from infectious hepatitis, chemical hepatitis, cirrhosis, or tumor metastasis and can resemble nitrosourea-induced hepatotoxicity. Cytopenias may reflect malignancy-associated myelofibrosis, autoimmune disorders, aplastic anemia, or anemia of chronic disease rather than nitrosourea-induced myelosuppression. Renal dysfunction requires consideration of acute kidney injury causes, such as prerenal azotemia and acute tubular necrosis. Altered mental status or focal neurologic findings may arise from intoxication, tumor recurrence, or delirium and can complicate recognition of nitrosourea-induced neurotoxicity.

Prognosis

Patients receiving nitrosourea therapy generally have a poor prognosis because high-grade gliomas have a median overall survival of less than 2 years. The mean overall survival of patients with glioblastoma multiforme and anaplastic astrocytoma was 14.1 months. Patients treated with lomustine had a 5.3-month survival gain, whereas patients treated with ACNU had an 8.9-month survival gain.[33]

The prognosis of nitrosourea-associated toxicity depends on the affected organ systems, severity of manifestations, and associated complications. Myelosuppression complicated by neutropenic sepsis may be life-threatening despite intensive treatment. BCNU-induced pulmonary fibrosis carries a particularly poor prognosis, with an estimated mortality rate of 30% to 40%. Preexisting pulmonary disease and a history of smoking increase the risk of pulmonary fibrosis following nitrosourea therapy.

Complications

Complications of nitrosourea toxicity include irreversible bone marrow suppression and fibrosis, irreversible pulmonary fibrosis with impaired pulmonary function, renal failure, and secondary leukemias. Clinical signs of hepatotoxicity generally resolve within several weeks, but liver biopsy may demonstrate hepatic necrosis for months. Patients receiving a cumulative carmustine dose greater than 1400 mg/m² have a significantly higher risk of pulmonary fibrosis. Pulmonary toxicity may manifest years after treatment and can be fatal, particularly in patients treated during childhood.

Deterrence and Patient Education

Patients receiving nitrosourea chemotherapy should receive education on the signs and symptoms of nitrosourea toxicity and instructions to seek emergency care for severe symptoms. Store nitrosoureas in a secure location out of reach of children to prevent accidental ingestion.

Pearls and Other Issues

Nitrosoureas are highly toxic yet effective chemotherapeutic drugs used to treat various malignancies, particularly glioblastomas. Delayed, dose-dependent myelosuppression is the most common adverse effect. Diffuse pulmonary fibrosis has been reported in 10% to 30% of patients treated with carmustine. Nitrosoureas can damage virtually every organ system, and no specific antidote exists for nitrosourea toxicity. Treatment consists of supportive care, blood product transfusions when indicated, and prophylactic antimicrobial administration in selected cases.

Enhancing Healthcare Team Outcomes

Adverse effects are common because nitrosoureas are cytotoxic. Managing nitrosourea toxicity requires an interprofessional healthcare team, including laboratory technicians, radiology technicians, blood bank technologists, and clinicians from various specialties. Specialist involvement depends on the affected organ systems. Emergency and primary care clinicians should recognize the signs and symptoms of nitrosourea toxicity and arrange urgent evaluation.

Hospitalists and hematologists treat patients requiring hospital admission, and oncology consultation is particularly important when myelosuppression occurs. Nephrology, hepatology, gastroenterology, neurology, pulmonology, and cardiology services may also participate in care, depending on the affected organ systems. Current guidelines recommend antibiotic and antifungal prophylaxis for patients with high-risk neutropenic fever. ESAs and blood transfusions are recommended for selected patients with myelosuppression-associated anemia.

Review Questions

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