Management of Chemotherapy-Induced Neurotoxicity

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Outline

- Review of pathogenesis of chemotherapy-induced neurotoxicity
- Clinical presentations of chemotherapy-induced neurotoxicity
- Management of chemotherapy-induced neurotoxicity

Neurologic Complications in Oncology Patients

- Cancer
- Procedure
- Therapy
  - Chemotherapy
  - Radiation therapy
  - Surgery
- Concurrent diseases
  - e.g. diabetes, renal dx, hypothyroidism, vitamin deficiency states, autoimmune dx, infectious dx, hereditary dx
- Concurrent medication/interaction
Neurologic Complications of Cancer Chemotherapy - Pathogenesis

- Peripheral nervous system toxicity
  - Sensory axon damage → degeneration and dying back of axons and myelin sheaths → damage of cell body
  - Sodium channel dysfunction
- Central nervous system toxicity
  - Toxic metabolites
  - Metabolic changes, end organ dysfunctions, fever, direct CNS drug toxicity

Commonly Used Anti-cancer Drugs Causing Central Neurotoxicity

- Ifosfamide
- Methotrexate
- Cisplatin
- Capecitabine

Commonly Used Anti-cancer Drugs Causing Peripheral Neurotoxicity

- Platinum Agents (cisplatin, carboplatin, oxaliplatin)
- Taxanes (paclitaxel, docetaxel, nanoparticle formulation of paclitaxel)
- Vinca alkaloids (vincristine, vinblastine, vinorelbine, vindesine)
- Thalidomide, Lenalidomide
- Bortezomib
- Procarbazine, cytarabine, etoposide, alfa-interferon
Central Nervous System Toxicity
Clinical Presentations

- Encephalopathy
  - with seizures
  - without seizures
- Transient aseptic meningitis
- Chronic leukoencephalopathy
- Cerebrovascular diseases (Stroke)
- Adjuvant therapies drug interactions or AEs

  - Ifosfamide, cisplatin
  - Capecitabine
  - IT methotrexate
  - Methotrexate
  - Cisplatin
  - Steroids, antiepileptic drugs

Peripheral Nervous System Toxicity
Clinical Presentations

- Chronic Peripheral neuropathy
  - Sensory
  - Sensory-motor

- Acute sensory neuropathy

  - Platinum agents
  - Taxanes
  - Vinca alkaloids
  - Thalidomide, Lenalidomide
  - Bortezomib

  - Oxaliplatin

Management of Chemotherapy-Induced Neurotoxicity
To start...........

- Screen for risk factors prior to starting chemo treatment
  - Preexisting neuropathy, diabetes, alcoholism, nutritional deficiency, HIV, immunosuppressive illnesses, congenital neuropathy, age?
  - Concomitant medications
  - Anticipated dose and administration of neurotoxic anti-cancer drugs
    - Vincristine > 4 mg; paclitaxel > 175-20 mg/m²; Docetaxel > 600 mg/m²; Cisplatin > 300-600 mg/m²; Carboplatin > 400 mg/m²; Oxiplatin > 175-200 mg/m²
    - Ifosfamide continuous infusion with ≥ 1500 mg/m²
  - Careful baseline examination and selection of evaluation tool(s)
  - Baseline labs
    - Blood glucose, thyroid function tests
  - Patient education
    - Glycemic control, alcohol consumption, avoidance of offending agents
Management of Chemotherapy-Induced Central Neurotoxicity

- Ifosfamide-induced encephalopathy
  - Due to neurotoxic metabolite, chloracetaldehyde
  - Dose and infusion rate-related
  - Decrease risk by using CI & dose fractionation
  - Methylene blue was tried but not recommended for routine use

Management of Chemotherapy-Induced Peripheral Neurotoxicity

- Acetyl-L-carnitine
  - MOA: regulation of acetyl-CoA, acetylation of tubulin, increase NGF-induced histone acetylation
  - Dose: 1 gm po tid
  - 1 gm IV over 1-2 hr
  - Clinical Experience:
    - cisplatin + paclitaxel, vincristine & oxaliplatin
    - Symptomatic and electrophysiological improvements

- Alpha-lipoic Acid
  - MOA: cyclic disulfide, a broad spectrum antioxidant. Also act to recycle other antioxidants (glutathione, vit C & vit E)
  - Dose: 600 mg IV q week
    - 600 mg po q day
  - Clinical Experience:
    - cisplatin + docetaxel, oxaliplatin
    - Symptomatic improvements

References:
Management of Chemotherapy-Induced Peripheral Neurotoxicity
Neuroprotective Agents

- **Amifostine**
  - MOA: thiophosphate cystamine analog with selective cytoprotective effect of non-tumor tissue
  - Dose: 740 mg/m² IV infusion
  - Clinical Experience:
    - Cisplatin, paclitaxel, carboplatin
    - Mixed results but severe hypotension reported

- **Carbamazepine**
  - MOA: anticonvulsant that acts as sodium channel inhibitor
  - Dose: 200 mg po tid
  - Clinical Experience:
    - Oxaliplatin
    - Mixed results (small studies)

- **Glutamine**
  - MOA: nonessential gluconeogenic amino acid that serves as main energy source of rapid proliferating cells and primary transporter of nitrogen between tissues, also up-regulates nerve growth factor mRNA
  - Dose: 10 gm po tid
  - Clinical Experience:
    - Paclitaxel
    - Symptomatic improvements

Management of Chemotherapy-Induced Peripheral Neurotoxicity Neuroprotective Agents

- **Glutathione (GSH)**
  - MOA: natural tripeptide with a high affinity for heavy metals
  - Dose: 1500 mg/m² IV over 15 mins prior to chemo
  - Clinical Experience:
    - Cisplatin, oxaliplatin
    - Symptomatic improvements & neuroprotection noted


- **Vitamin E (α-tocopherol)**
  - MOA: Antioxidant that exerts a protective function on biologic membranes. Low serum conc of α-tocopherol was observed in pts with neuropathy
  - Dose: 300 - 600 mg/day pop
  - Clinical Experience:
    - Cisplatin
    - Symptomatic improvements and neuroprotection noted


- **Calcium and Magnesium Infusion**
  - MOA: stabilize the cell membrane associated with oxaliplatin-induced disruption of sodium channels which increase excitability of sensory nerves
  - Dose: 1 gm calcium gluconate + 1 gm magnesium sulfate before and after chemo
  - Clinical Experience:
    - Lower severity of neuropathy
    - Recent data from CONCEPT trial discourage the continual use of this approach, especially in adjuvant setting

Management of Chemotherapy-Induced Peripheral Neurotoxicity

Neuroprotective Agents

- Multi-B complex vitamins
- N-acetylcysteine
- Diethyldithiocarbamate (DDTC)
- Melatonin
- Venlafaxine
- Sodium thiosulfate
- Corticosteroids
- Nimodipine
- ORG-2766 (ACTH 4-9)
- Recombinant human leukemia inhibitory factor (HLIF)

Conclusions

- Neurotoxicity remains a dose-limiting toxicity of anti-cancer chemotherapy.
- Several agents appear promising.
- Current treatments are largely based on case reports and only 15 agents have been studied in clinical trials. Many of these trials are limited with small N, study designs, non-standardized outcome measures.
- Future studies must possess better study design, standardization of grading scales and outcome measures including QOL.