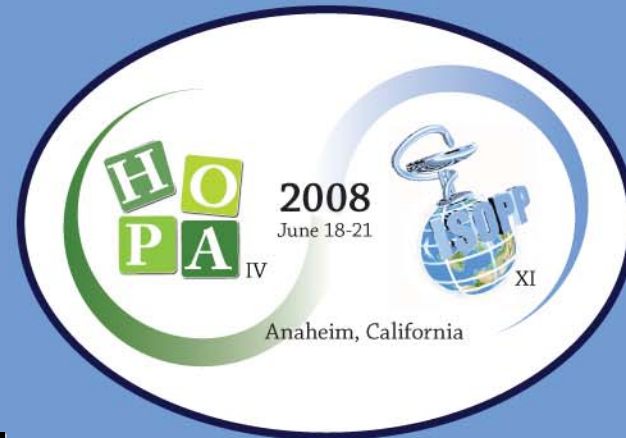


Therapeutic Challenges in Pediatric Cancer

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Disclosure

- John N. McCormick, PharmD, BCNSP has no real or apparent conflicts of interest to report

Learning Objectives

- Discuss chemotherapy adherence issues in children
- Describe methods used to measure/assess adherence
- Discuss methods for improvement
- Review methotrexate-induced neurotoxicity
- Discuss therapeutic interventions

Example Case

- TJ is a 6-year-old low-risk ALL patient in week 83 of maintenance. Therapy consists of methotrexate (MTX) (40 mg/m²) IM q week and 6-mercaptopurine (6-MP) (75 mg/m²) oral suspension PO daily. He has had no signs or symptoms of toxicity related to therapy. This visit, the clinician on service asks you to check 6-thioguanine nucleotide (6-TGN) concentrations and review his white blood count (WBC) and absolute neutrophil count (ANC) for increasing trends as protocol goal parameters per week are:

WBC <3.0 μ L and ANC <1500 mm³

Example Case

Week	6-MP/MTX	WBC (μL)	ANC (mm^3)
75	Yes	2.8	1460
76	Yes	2.1	1200
77	Yes	4.3	3100
78	Yes	1.9	1100
79	Yes	4.9	2750
80	Yes	5.3	3200
81	Yes	5.5	3600
82	Yes	4.8	3200
83	Yes	4.5	3380

Example Case

■ Results:

- Elevated WBC/ANC >60% of weeks reviewed (WBC >3.0 μL /ANC >1500 mm^3)
- 6-TGN: 55 pmol/ 8×10^8 (100–500)

■ Diagnosis:

- Adherence problems associated with 6-MP

Adherence to Medication

“Drugs don’t work in patients who don’t
take them”

C. Everett Koop, MD, former US Surgeon General

Adherence

- Extent to which patients take medications as prescribed by health care professional
- Reported as percentage of prescribed doses taken during a specific period
- Decreases significantly with chronic conditions
 - (HIV, asthma, hypertension, cancer)
- Higher early in treatment courses in clinical trials
 - New diagnosis, increased attention, clinic visits

Problems With Nonadherence in Clinical Trials

- Unnecessary tests/increased cost
 - 6-TGN, CBC-diff, readmission
- Unwarranted dosing changes
- Decreased therapeutic efficacy
- Relapse
- Decreased event-free and overall survival

Risk Factors for Decreased Adherence

- Age
- Chronic conditions
- Cognitive impairment
- Low literacy, social support
- Poor clinician-patient relationship
- Complex treatments and directions
- Cost

Predictors of Poor Adherence in Children

- Dosing frequency
- Complex regimens
- Formulations
 - Large tablets, bitter liquids, gritty powders

Predictors of Poor Adherence in Children

- Side effects
 - Nausea/vomiting, taste alterations, skin rash
 - Drug interactions
- Caregivers' understanding/support
- Language barrier
- Fear/embarrassment

Adherence Measures for Predicting Success

- No standards for success
 - >80% acceptable
 - Hypertension
 - >95% mandatory
 - HIV
 - Cancer?
 - Is anything <100% acceptable?

Adherence and Cancer

- Oral chemotherapy available for children:

Busulfan

Cyclophosphamide

Dasatinib

Imatinib

Erlotinib

Etoposide

Hydroxyurea

Mercaptopurine

Methotrexate

Mitotane

Sorafenib

Thioguanine

Tretinoin

Temozolomide

Methods for Measuring Adherence

- Direct methods
 - Directly observed
 - Monitor medication or metabolite blood concentrations
 - Measure biologic markers in blood

Methods For Measuring Adherence

- Indirect methods
 - Patient self reports/questionnaires/diaries
 - Pill counts
 - Rates of prescription refills
 - Electronic medication managers

Tips for Improving Medication Adherence: Clinician

- Pharmacist to educate, reinforce, and provide patient medication handouts
- Prescribe medications given once or twice daily
- Keep documentation in patient's chart for clinician to monitor (patient contracts, etc)

Tips for Improving Medication Adherence: Clinician

- Make patient a partner in his/her treatment
- Reinforce adherence at each visit
- Consider financial impact
 - Use generics if available

Tips for Improving Medication Adherence: Patient/Family

- Incorporate dosing into daily routine
- Keep tally sheet, mark a calendar, use a pillbox
- Use visual reminders (notes on refrigerator or medication cabinet/mirror)
- Set alarm on watch or clock

Tips for Improving Medication Adherence: Patient/Family

- Ask friends or other family to remind you
- Parents can offer children rewards for remembering
- Pager systems
- Microelectronic memory systems

What Happened With TJ?

- Family counseling session determined the following:
 - Lives with mom and grandmother
 - Mom back working evening shift as LPN, needs \$\$
 - TJ says he is “tired of the taste and taking medicine every night”
 - Grandmother with arthritis: has difficulty with drawing up suspension in oral syringe
 - Grandmother “rewarded” TJ with ice cream or chocolate pudding

What Happened With TJ?

- Adherence issues:
 - Single parent, stressed household
 - Chronic phase
 - Formulation
 - Caregiver understanding
 - Drug interaction

TJ: Interventions

- Changed to tablet formulation
 - Educated family/TJ on crushing/mixing
- Increased TJ's involvement with care
 - Provided him with personal "medication watch" with alarm set every evening for 6-MP dose
 - Allowed to operate the tablet crusher
- Changed to nondairy "reward" system
 - Stickers, gummy bears
- Increased monitoring of 6-TGN concentrations

Pediatric Challenges – Adherence

- Increasing number of oral chemotherapy regimens in pediatric cancer
- Need for multiple formulations or methods for delivery
 - Recipes anyone?
- Anticipate nonadherence and be ready to intervene

Methotrexate Neurotoxicity

Example Case

- TP is 13-year-old male with standard risk ALL. He recently received consolidation therapy with intrathecal MTX and high-dose MTX (HDMTX) @ 5 gm/m² over 24 hours. He complained of a headache on day 2 that resolved. He had delayed elimination (90-hour level=0.03 uM). He returned to clinic 10 days after start of HDMTX feeling “jerky” and “weird” inside with slurred speech, weakness, and paraesthesia of all 4 extremities. Also was emotional (laughing and crying in quick succession) with mild left hemiparesis
- Impression: encephalopathy related to methotrexate

Types of Methotrexate Neurotoxicity

- Acute/immediate
 - “Chemical arachnoiditis”
- Subacute
 - Stroke-like syndrome
- Chronic/delayed
 - Leukoencephalopathy

Risk Factors for MTX Neurotoxicity

- Age
- Radiation therapy
- Higher CSF concentrations
- Frequency of dosing
- Injection method

Acute MTX Neurotoxicity

- Presentation
 - Aseptic meningitis
 - Headache, nuchal rigidity
 - Transverse myelopathy
 - Acute encephalopathy
- Occurs: 2 to 4 hours postinjection
- Duration: 2 to 3 days

Subacute MTX Neurotoxicity

■ Presentation

- Visual disturbances, sensory deficits
 - Confusion, disorientation
 - Somnolence
 - Ataxia, spasticity, seizure
 - Paraplegia, hemiparesis
- ## ■ Occurs 5 to 10 days post systemic therapy

Chronic/Delayed MTX Neurotoxicity

- Presentation
 - Personality changes
 - Confusion
 - Somnolence
 - Progressive dementia
 - Aphasia
 - Coma

Chronic/Delayed MTX Neurotoxicity

- Leukoencephalopathy
 - Pathology
 - Demyelination
 - Axonal destruction
 - Coagulation necrosis

Subacute Neurotoxicity

- Proposed mechanism
 - Decreased dopamine/serotonin production
 - Inflammation
 - Increased homocysteine
 - Increased adenosine in CSF

Homocysteine Effect

- Concentration increased in both plasma and CSF
- Directly toxic to vascular endothelium
- Excitatory agonist on NMDA receptors

Homocysteine Effect

- 53 children newly diagnosed with ALL
- Plasma and CSF homocysteine samples with each course of consolidation HDMTX (5 g/m² or 2.5 g/m² weekly x 2)
- Plasma samples collected at diagnosis, before HDMTX course 1, 2, and at hr 23 and 44 from start of course 2 (before leucovorin rescue begun)
- CSF samples at diagnosis, before HDMTX

Homocysteine Effect

■ Results:

- Plasma levels trended up with MTX
- 9 patients with neurotoxicity (seizure)
 - Trend with increased plasma homocysteine and seizure
 - No relationship between CSF homocysteine and seizure

Treatment Options for Homocysteine-Related Neurotoxicity

- Dextromethorphan
 - NMDA receptor antagonist

Dextromethorphan Treatment for Homocysteine Effect

- 5 patients with severe subacute toxicity (dysarthria/hemiplegia)
- Elevated CSF homocysteine
- Dextromethorphan at 1 to 2 mg/kg orally

Dextromethorphan Treatment for Homocysteine Effect

- Results: all patients experienced resolution of symptoms within 3 hours
- Caution: be aware of potential drug interactions

Additional Treatment Options for Homocysteine Effect

- Leucovorin or folic acid
- Vitamin B6 (pyridoxine)
- Vitamin B12 (cyanocobalamin)
- Trimethylglycine (betaine)

MTX and Adenosine

- Increased release of adenosine from fibroblasts and endothelial cells secondary to MTX inhibition of purine synthesis

Adenosine Effect

- Dilates cerebral blood vessels
- Slows release of neurotransmitters at presynaptic junctions
- Modifies postsynaptic response
- Slows discharge rates of neurons

Adenosine Effect

- 6 patients with ALL or lymphoma with MTX neurotoxicity
- Elevated CSF adenosine levels
- No predictable relationship between dose of MTX and CSF adenosine level

Aminophylline Treatment for Adenosine Effect

- Mechanism:
 - Direct antagonist adenosine
- Dose:
 - 2.5 mg/kg IV over 1 hour
 - 2.5 mg/kg IV over 12 hours
 - 2.5 mg/kg PO theophylline
- Result:
 - 4/6 with complete resolution within 30 minutes

Considerations for MTX Neurotoxicity

- Clinical pharmacy expertise with therapeutic drug monitoring for MTX
- Prospective diagnostic imaging in patients receiving methotrexate
- Increased awareness and monitoring of homocysteine plasma/CSF levels
- Early intervention with presenting signs/symptoms of neurotoxicity