Management of ECD Symptoms and Side Effects of Treatments

The Dark Side of the Moon

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Agenda

- Urological treatments
- Diabetes Insipidus
- Pain Management
- Interferon-α
- Anakinra
- Vemurafenib
- Our experience
Urologic Treatments

- Ureteral stenting
  - Mono or bilateral
  - Stabilize hydronephrosis and CKD
  - LUTS in almost 45% pts
    - Mostly due to stent irritation
    - Colonization
      - Require prophylactic antibiotic treatment (MDR)
      - Schedule ureteral stenting replacement
  - Infection
    - Monitor drug interaction
    - 1 – 3 months ureteral stenting procedure
Diabetes Insipidus

- Desmopressin (dDAVP)
  - Intranasal (pref), oral, sublingual or parenteral
  - Decreased absorption with meals (40 – 50%)
  - 5% absorbed from the gut
  - 0.1 mg intranasal ≈ 2.5 – 5 mg oral
  - Initial dose 0.05 mg bedtime → 0.1 – 1.2 mg/day

- Long-term data
  - No attenuation of antidiuretic effect
  - No side effect
  - No antibody formation
Pain Management

- **Acetaminophen**
  - First-line up to 4 g/day
  - Combined with opioid medications to reduce the amount of opioid needed

- **NSAIDs**
  - Avoid if CKD
  - Interference with platelet aggregation
  - Evaluate cardiovascular risk factors

- **Opioid**
  - Start with low dose of immediate-release/short-acting agents
  - Titrate the dose by slowly increasing it
    - No > than 25 – 50 % of the total daily dose
  - Tramadol and tapentadol
    - μ and monoamine receptors
    - Neuropathic and chronic musculoskeletal pain
Opioid Side Effects

- Monitor patients for
  - Constipation, nausea and vomiting
    - Laxative prescription
    - Combination with naloxone
    - Titrate the dose slowly
  - Sedation, impaired psychomotor function
    - Reduce dosage
    - Avoid combination with sedative and monoamine antagonist drugs
- Urinary retention
  - Prefer short half-life agents (fentanyl)
  - Combination with naloxone
**Interferon-α**

- **Standard dose**
  - IFNα 9 mIU/wk (3 injections weekly)
  - PEG-IFNα 135 μg/wk

- **High dose**
  - IFNα ≥ 18 mIU/wk (3 injections weekly)
  - PEF-IFNα ≥ 180 μg/wk

*No significant difference in side effects between standard and high dose*

**Tolerance with high-dose**
- 54% no adverse events
- Severe asthenia 41%
- Myalgia 15%
- Thrombocytopenia 4%
- Depression 8%
- Discontinuation 13%
Management of IFN-α S.E.

- “Flu”-like symptoms
  - Napping and resting when required
  - Maintaining daily schedule and keeping active
  - Acetaminophen
    - 1 g 1 hour before injection and 3-4 hours after
  - Judicious timing
    - Predictable time after injection

- Injection site irritation
  - Inject with sufficient force
  - Beyond the superficial skin layer into sc tissue
  - Rotate injection site
Management of IFN-α S.E.

- Neuropsychiatric manifestations
  - Depression
    - Up to 16% of pts
    - Suicidal thoughts in 4 – 6% of pts
    - True suicidal ideation → discontinuation and psychiatrist
  - Mild depression
    - Citalopram 20 mg → titrated upwards
    - Psychological and psychiatric support

- Fatigue
  - Adequate fluid balance
  - Behavioral strategies
  - Social support network
  - Paroxetine
Anakinra

- Remarkable record of safety
  - Short half-life of 6 h → prompt discontinuation
- Risk for virus-type, non-life-threatening upper airway infections
- Rare opportunistic infections
- Daily s.c. administrations
  - Often cause injection site reactions
  - Usually resolve within 14 days
  - Topical steroid
  - Anti-H1 drugs
Vemurafenib: skin toxicities

- Folliculocentric eruption
- Maculopapular "toxic erythema"
- Eruptive squamous papillomas
- Phototoxicity
- Hyperkeratosis
- Patchy papular eruption
- Erythematous plaque (T-cell lymphoma)
Vemurafeninb: skin toxicities

Photosensitivity

Keratoacanthoma

SCC
Management Skin Toxicities

- **Erythema nodosum-type rash**
  - Emollients, topical steroids, analgesia
  - Consider oral steroids: prednisolone 0.5 mg/kg/day (up to 60 mg/kg/day) for 5–7 days [Sinha et al. 2012]
  - Consider interrupting KI
  - Seek dermatology advice

- **Photosensitivity**
  - Prophylactic sunscreen SPF >30 (UVB) plus 5* (UVA) rating; cover up
  - Treat burns as appropriate

- **Squamous papillomas/warts**
  - If problematic, refer to dermatologist for cryotherapy or curettage

- **Keratoacanthoma, SCC**
  - Refer urgently to dermatologist for intervention, particularly if rapidly enlarging or symptomatic

- **Dry skin**
  - Soap substitutes, emollients

- **Folliculitis or cysts**
  - Soap substitutes
  - Antibiotics – topical or systemic
  - Consider excision for symptomatic, uninfected cysts
Vemurafenib: diarrhoea

- Common side effect: 25% incidence
- Mild to moderate
- Mainly outpatient
- Dietary modifications
  - Bananas
  - Rice
  - Apples
  - Toast
- Stop lactose-containing products
Vemurafenib: Osteoarticular

- Arthralgia usually in the first months
- Incidence 56%
- Any joint can be affected
  - Usually small joints
- Pain may be intermittent or constant
- May be self-limiting
- Good response to NSAIDs and steroid
Vemurafenib: cardiac

- QTc prolongation
  - Observed in 2% of pts in registration studies*
    - 2 pts developed cardiac arrhythmia
      - Both had hypertension and ischaemic heart disease
    - Median time to development 1.9 months
  - Always check magnesium levels
    - Treatment not recommended in pts with known low Mg
  - Check QTc before starting vemurafenib
    - <500 ms

- Hypertension
  - Check regularly blood pressure

* Pts treated for stage IV melanoma
Management of Cardiac Side Effects

- **QTc > 500 ms at baseline**
  - Treatment not recommended

- **QTc increase meets values of both >500 ms and >60 ms change from pretreatment values**
  - Permanently discontinue BRAFi
  - Interrupt BRAFi until QTc < 500 ms
  - Correct electrolyte abnormalities if present
  - Address any cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias)
  - Resume BRAFi at reduced dose level
  - If recurs despite two dose reductions, discontinue BRAFi

- **QTc > 500 ms but <60 ms change from baseline**

- **QTc < 500 ms but >60 ms change from baseline**
  - Interrupt treatment until QTc returns to <60 ms change from baseline
  - Correct electrolyte abnormalities
  - Address cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias)
  - Resume at reduced dose level
  - If recurs despite two dose reductions, discontinue treatment
Vemurafenib: kidney

Mean ±SD creatininemia in AKI+ group (µmol.L⁻¹)

Times in months

M0: Introduction of VMF
M10: Discontinuation of VMF
Our Experience

- 12 patients treated with vemurafenib
  - 2 interruptions
    - Diffuse skin vasculitis (after 1 week)
    - Increased CKD and dialysis (after 3 months)
  - 1 dose reduction
    - Transitory
    - AKI (2 x)

- Side Effects
  - Osteoarticular side effects
    - 6 patients (all before starting our protocol)
  - Kidney
    - Creatinine 1.5 x in 3 patients
  - Hypertension
    - 1 patient
    - Transitory (6 months)
  - Skin
    - Rash 2 patients (all before starting our protocol)
How we manage it

- Start low-dose corticosteroid therapy
  - PDN 15 mg die for 5 days
  - PDN 10 mg die for 5 days
  - PDN 5 mg die

- If adverse cutaneous reaction of grade 1-2 or increase in serum creatinine (<50%)
  - → No dose adjustment

- If adverse cutaneous reaction of grade 3 or increase in serum creatinine (>50% <100%)
  - → Dose reduction to vemurafenib 50% (75%)

- Dose interruption
  - Dalysis
  - Cutaneous grade 4
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