Management of ECD Symptoms and Side Effects of Treatments

The Dark Side of the Moon

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OSPEDALE SAN RAFFAELE
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO

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

- Acetamoniphen
  - First-line up to 4 g/day
  - Combined with opiod medications to reduce the amount of opioid needed
- NSAIDs
  - Avoid if CKD
  - Interference with platelet aggregation
  - Evaluate cardiovascular risk factors
- Opiod
  - Start with low dose of immediate-release/short-acting agents
  - Titrate the dose by slowing 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

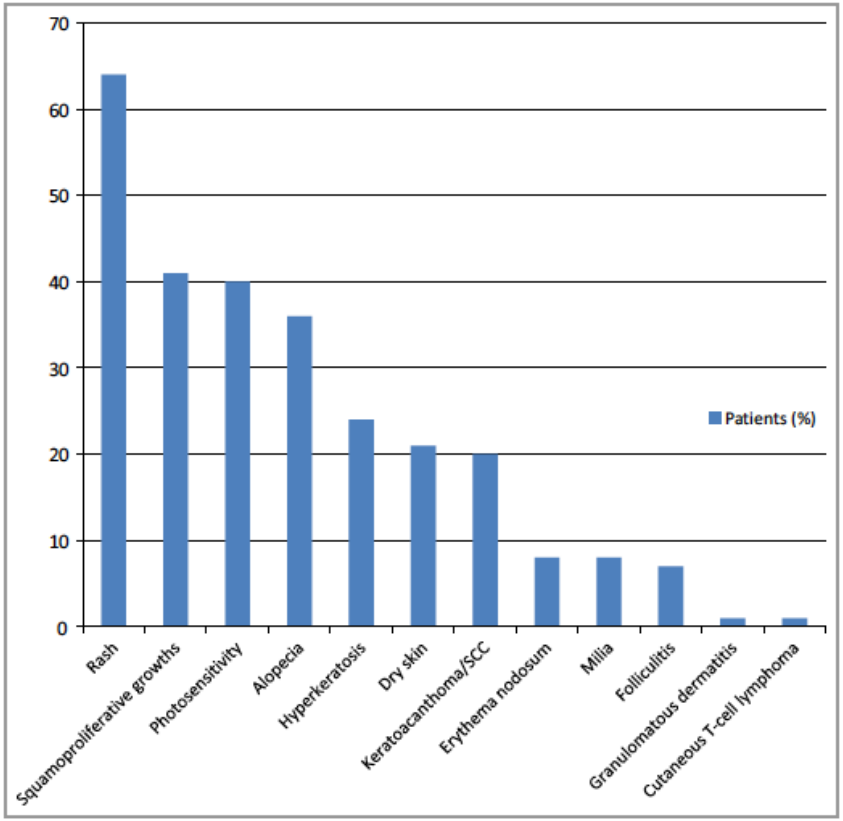
Management of IFN-α S.E.

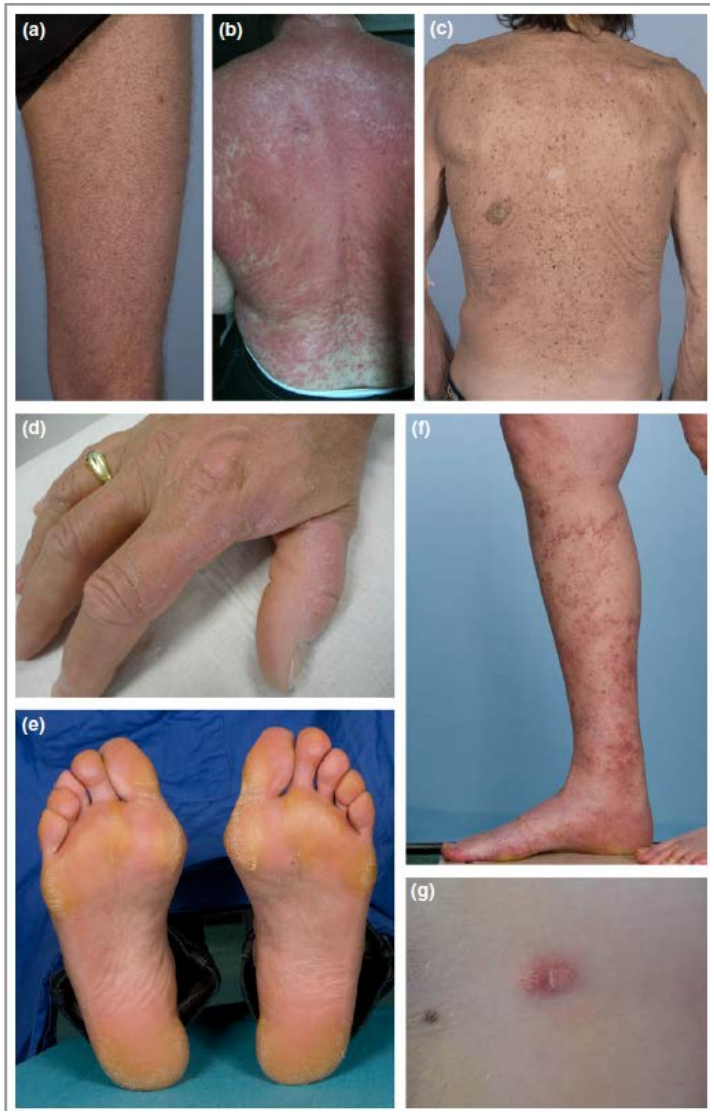
- Neuropsychiatric manifestations
  - Depression
    - Up to 16% of pts
    - Suicidal thoughts in 4 – 6% of pts
    - True suicidal ideation → discontinution and psychiatrist
    - Mild depression
      - Citalopram 20 mg → titrated upwards
      - Psychological and psychiatric support
  - Fatigue
    - 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 opportunist infections
- Daily s.c. administrations
  - Often cause injection site reactions
  - Usually resolve within 14 days
  - Topical steroid
  - Anti-H1 drugs

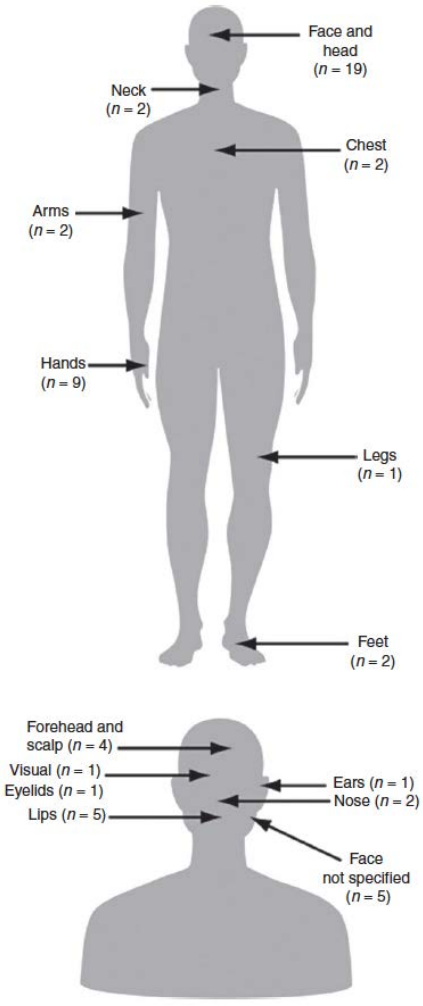
Vemurafenib: skin toxicities



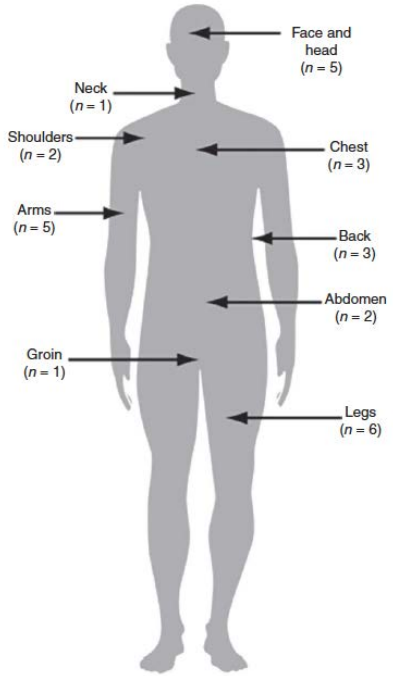


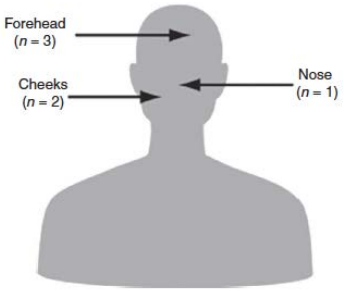
a) Folliculocentric eruption
b) Maculopapular “toxic erythema”
c) Eruptive squamous papillomas
d) Phototoxicity
e) Hyperkeratosis
f) Patchy papular eruption
g) Erythematous plaque (T-cell lymphoma)

Vemurafeninb: skin toxicities



Photosensitivity





Keratoacanthoma
SCC

Management Skin Toxicities

Erythema nodosum-type rash	• Emolients, 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, emolients
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

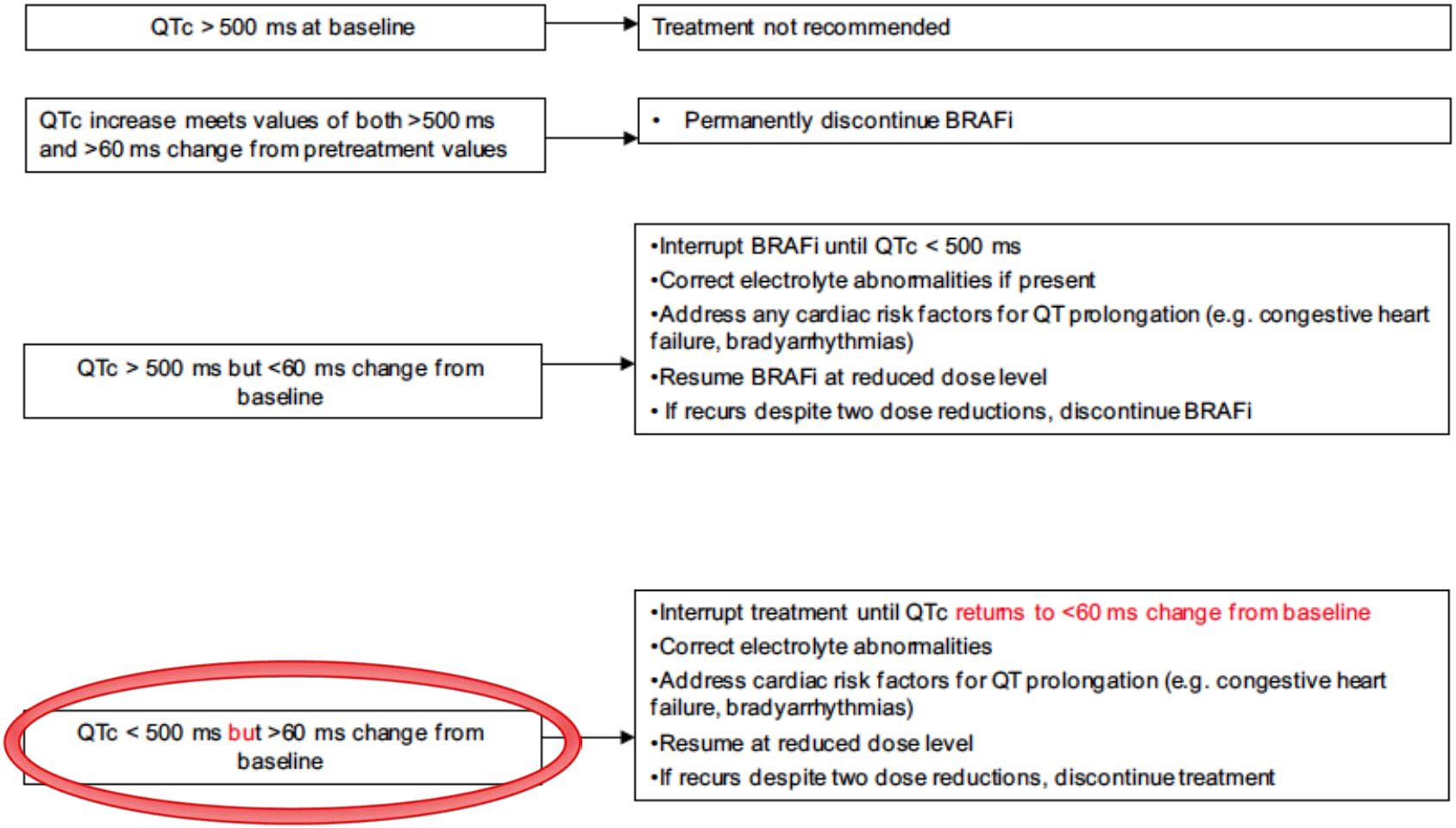
- Arthralgia usually in the first months
- Incidence 56%
- Any joint can be affected
  - Usually small joints
- Pain may be intermittent or constant
- May be self-limiting
- Good response to NSAIDs ad steroid

Vemurafenib: cardiac

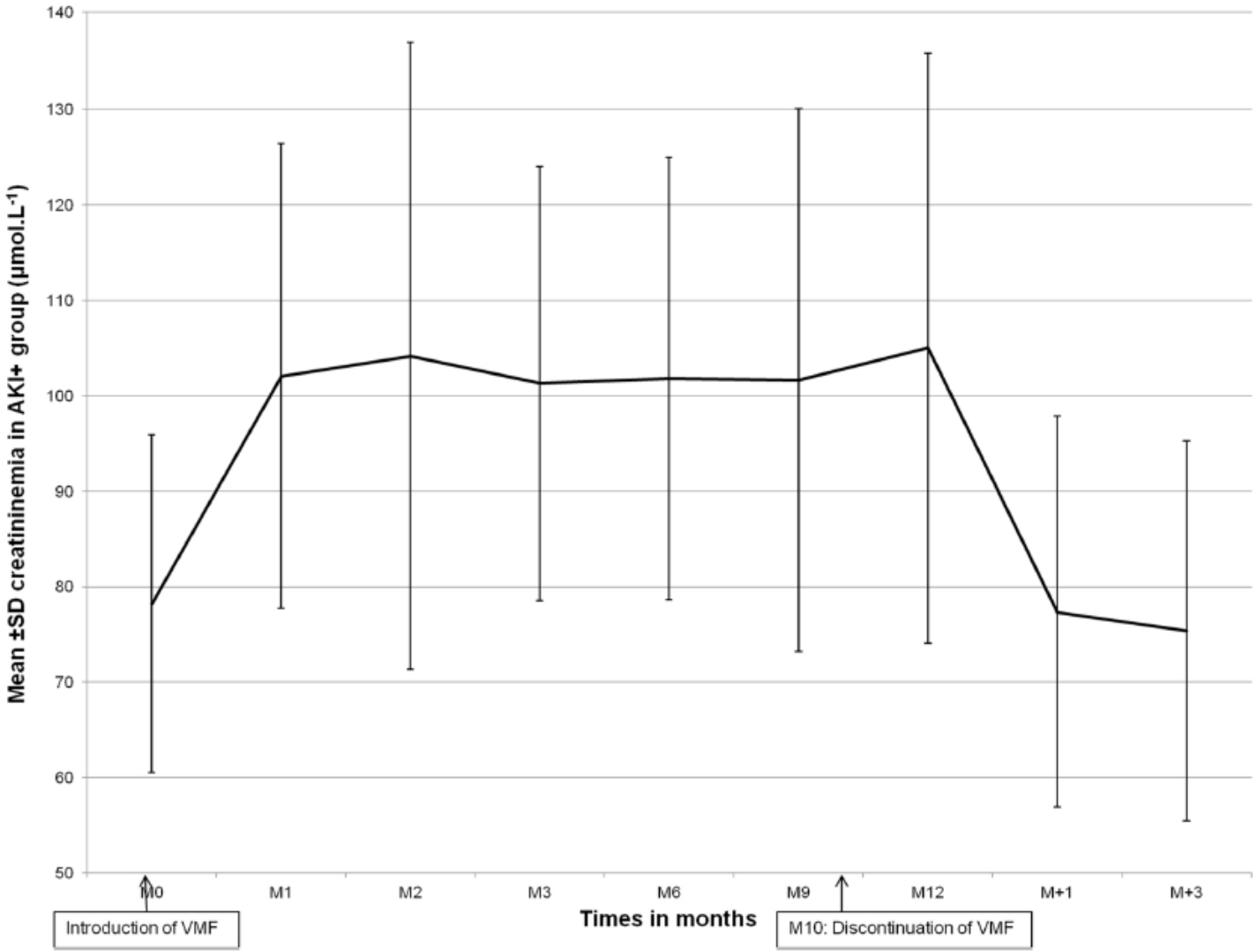
- QTc prolungation
  - Observed in 2% of pts in registration studies*
    - 2 pts developed cardiac arrhytmia
      - Both had hypertension and ischaemic heart disease
    - Median time to development 1.9 months
    - Always check magnesium levels
      - Treatment not recommended in pts with known low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

* Pts treated for stage IV melanoma

Management of Cardiac Side Effects



Vemurafenib: kidney



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

Thanks to

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