Care Step Pathway - Skin Toxicities

Assessment

Look:
- Does the patient appear uncomfortable?
- Does the patient appear unwell?
- Is there an obvious rash?
- Is the patient scratching during the visit?
- Is skin integrity intact?
- Are there skin changes?
  - Xerosis (dry skin)
  - Changes in skin pigment or color
- Is there oral involvement of the rash?
- Does the rash involve the genital-vaginal region? The scalp?

Listen:
- Does the patient have pruritus with or without rash?
- Is there a rash with or without pruritus?
- Are symptoms interfering with ADLs?
- With sleep?
- Have symptoms worsened?

Recognise:
- Is there a history of dermatitis, pre-existing skin issues (psoriasis, eczema, wounds, prior radiation to region, etc.)?
- Pathology abnormalities consistent with other etiologies (e.g., eosinophils on complete blood count, liver function abnormalities)

Grading Toxicity

MACULOPAPULAR RASH (aka morbilliform rash)

Definition: A disorder characterised by the presence of macules (flat) and papules (elevated); frequently affecting the upper trunk, spreading towards the center and associated with pruritus

Grade 1 (Mild)
Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)

Grade 2 (Moderate)
Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); having psychological effect and limiting instrumental ADLs; rash covering >30% BSA with or without mild symptoms

Grade 3 (Severe)
Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADLs; skin sloughing covering <10% BSA

Grade 4 (Potentially Life-Threatening)
Papules/pustules covering any % BSA with or without symptoms and associated with superinfection requiring IV antibiotics; skin sloughing covering 10-30% BSA; Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulcerations or necrotic bullous, haemorrhagic manifestations

Grade 5 (Death)

PRURITUS

Definition: A disorder characterised by an intense itching sensation

Grade 1 (Mild)
Mild or localized; topical intervention indicated

Grade 2 (Moderate)
Widespread and intermittent; skin changes from scratching (e.g., oedema, papulation, excoriations, lichenification [thick, leathery skin], oozing/crusts); limiting instrumental ADLs; oral intervention indicated

Grade 3 (Severe)
Widespread and constant; limiting self-care ADLs or sleep; systemic corticosteroid or immunosuppressive therapy indicated

Grade 4 (Potentially Life-Threatening)

Management

Overall Strategy
- Assess for other etiology of rash: ask patient about new medications, herbals, supplements, alternative/complementary therapies, lotions, etc.

Intervention in at-risk patients
- Advise gentle skin care:
  - Use moisturizing, soap-free wash, (fragrance-free, colour-free)
  - Use preservative-free, pH-balanced moisturizing creams (eg, sorbolene creams)
  - Apply moisturizers and emollients in the direction of hair growth to minimize development of folliculitis
- Advise sun-protective measures (at least 50+ SPF sunscreen)
- Assess patient & family understanding of prevention strategies and rationale
  - Identify barriers to adherence

Grade 1 (Mild)
- Immunotherapy to continue
- Oral antihistamines will be used in some patients
- Moderate potency topical corticosteroids may be used in some patients
- Consider a referral to a dermatologist
- If symptoms persist for 1-2 weeks or recur, withhold treatment and consider skin biopsy and oral corticosteroids
- Advise vigilant skin care
  - Increase to twice daily applications of non-steroidal moisturizers or emollients applied to moist skin
  - Moisturizers with ceramides and lipids are advised
  - Soothing methods
    - Cool cloth applications
    - Topicals with cooling agents such as menthol or camphor
    - Refrigerating products prior to application
  - Avoid hot water; bathe or shower with tepid water
  - Keep fingernails short
  - Cool temperature for sleep
- Advise strict sun protection (at least 50+ SPF sunscreen)
- Monitor vigilantly. Instruct patient & family to call clinic with any sign of worsening rash/symptoms. Anticipate office visit for evaluation
- Assess patient & family understanding of skin care recommendations and rationale
  - Identify barriers to adherence

Grade 2 (Moderate)
- Consider holding pembrolizumab or nivolumab and monitor for improvement weekly. If no improvement within 1-2 weeks or symptoms recur, consider skin biopsy and begin treatment with prednisone 1 mg/kg tapering over 4 weeks
- Ipilimumab will be withheld for any Grade 2 event
- High-potency topical corticosteroids to be used
- Oral corticosteroids* (0.5 mg/kg–1.0 mg/kg) and oral antihistamines/oral anti-pruritics can be used (high-potency topical corticosteroids can be considered for rash alone)
- Consider dermatology consult
- Patient education:
  - Proper administration of oral corticosteroids
    - Take with food
    - Take early in day
    - Concomitant medications may be prescribed
      - ➢ H2 blocker
      - ➢ Antibiotic prophylaxis
- Advise vigilant skin care
  - Gentle skin care
  - Tepid baths; oatmeal baths
- Advise strict sun protection (at least 50+ SPF sunscreen)
- Assess patient & family understanding of toxicity and rationale for treatment hold
  - Identify barriers to adherence

Grades 3/4 (Severe or Life-Threatening)
- Nivolumab or pembrolizumab to be withheld for any Grade 3 (severe) and discontinued for Grade 4 (life-threatening) skin conditions or confirmed SJS or TEN; Ipilimumab to be permanently discontinued for any Grade 3/4 event
- High-potency topical corticosteroids to be used; anticipate hospitalisation and initiation of IV corticosteroids* (0.1-1 mg/kg/day)
- Urgent dermatology consult +/- biopsy
- Provide anticipatory guidance:
  - Rationale for hospitalisation and treatment discontinuation
  - Rationale for prolonged steroid taper
  - Side effects of high-dose steroids
  - Risk of opportunistic infection and need for antibiotic prophylaxis
  - Effects on blood sugars, muscle atrophy, etc.
- For Grade 3/4 pruritus
  - Corticosteroid* dose 0.5-1.0 mg/kg/day
  - Consider GABA agonist, aprepitant, or omalizumab
- Assess patient & family understanding of toxicity and rationale for treatment discontinuation
  - Identify barriers to adherence, specifically adherence with steroids when transitioned to oral corticosteroids

*Administering Corticosteroids:

Steroid taper instructions/calendar as a guide but not an absolute
- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need & symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down & report them (taper may need to be adjusted)

Long-term high-dose steroids:
- Consider antimicrobial prophylaxis
- Consider additional antiviral and antifungal coverage
- Avoid alcohol/acetaminophen or other hepatoxins
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

RED FLAGS:
- **Extensive rash (>50% BSA), or rapidly progressive**
- **Anal, genitourinary, vaginal, or any mucous membrane involvement**
- **Concern for suprainfection**

ADLs = activities of daily living; BSA = body surface area; po = by mouth; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis