Targeted therapies

- Emergence in 1990s
- Higher efficacy for cancer treatment
- Decreased systemic toxicities
- Shift in dermatologic toxicity reporting
  - ‘rash’ -> ‘acneiform eruption’
  - ‘lesion’ -> ‘atypical keratosis’

Significance

- Quality of Life
  - Symptoms, emotional impact -> Acneiform eruption
  - Pain scale -> Hand-foot reactions
- Dose reduction or treatment interruption
  - 76%, EGFR inhibitors
  - 70% patients (reduction), 30% (discontinuation)
- Predicting severe skin reactions
  - Lapatinib-capectabine
  - Higher capectabine doses, brain metastases, 5HT3 antiemetics
  - Treat proactively
Acneiform eruption

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- VEGF inhibitors
- RET inhibitors

- Treatment options:
- *Doxycycline 100 mg BID
- *Hydrocortisone 2.5%
- *Bland emollient
- IL kenalog
- Oral prednisone
- Topical or oral retinoid
- *Prophylactic tx
- Dose reduction/cessation

Acneiform eruption

- Mechanism
  - EGFR expressed in undifferentiated basal keratinocytes
  - Blockade causes
    - Early differentiation (increased KRT1, STAT3, p27)
    - Decreased replication (downregulated Ki67, MAPK)
    - Increased inflammatory cytokines -> apoptosis
  - Thin stratum corneum, abnormally differentiated epidermis, dyskeratosis
  - Follicular rupture -> Inflammation and Pustules

Keratinocytic neoplasms

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- Hedgehog pathway inhibitors

- Treatment options:
- Reactive:
  - Cryotherapy
  - Electrodesiccation and curettage
  - Excision/Mohs
- Preventative
  - Oral retinoid
  - MEK inhibitor
  - Photodynamic therapy
  - Topical 5-FU
BRAF inhibitors

- Squamous papillomas
  - Hypertrophic actinic keratoses, irritated seborrheic keratoses, verruca
- Cutaneous squamous cell carcinoma
  - Vemurafenib: 25%
  - Dabrafenib: 7%
  - Mechanism: activates mutated HRAS
  - Treatment: destructive methods vs MEK inhibitor vs acitretin


Hand foot skin reaction (HFSR)

Distinct from hand-foot syndrome (HFS) or acral erythema (AE)

HFS/AE:
- Doxorubicin, 5-fluorouracil, capecitabine
- Diffuse erythema and edema

HFSR:
- Tender, erythematous focal plaques (weight-bearing or friction)
- Hyperkeratosis or bullae

Hand foot skin reaction

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- VEGF inhibitors

Treatment options:
- Preventative foot care (orthotics, shaving calluses/bunions)
- Topical keratolytics (urea, lactic acid)
- Clobetasol 0.05%
- Dose reduction/cessation

Hand-foot skin reaction

- **Mechanism**
  - VEGFR-related
  - Worse with beclizumab
  - Pressure and trauma with poor repair
  - Fas/Fasl mediated
  - Blocked with anti-FasL antibody
  - Same mediators as SJS/TEN

- **Risk factors**
  - Increased: Female, liver metastases, WBC > 5.5, 2 or more organs involved
  - Decreased: Lung metastases, good performance status

Melanocytic neoplasms

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors

- **Treatment options:**
  - Skin exams

Melanocytic neoplasms

- Eruptive lentigines
  - Higher Cyclin D1 expression
  - MAPK pathway upregulation
  - Higher degree of atypia

- New primary melanoma
  - 5/468 patients, Phase II/III
  - Wild-type BRAF, all < 0.5 mm
  - Mechanism: activates MAPK signaling pathway for wild-type BRAF

- < 10% of patients required dose interruption
Paronychia

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors

- Treatment options:
  - Treat superinfections
    - Oral antibiotics
    - Topical mupirocin and azole
  - ½ water: ½ vinegar soaks
  - Betamethasone 0.05% lotion*
  - Oral doxycycline
  - Nail avulsion
  - Phenol chemical matricectomy*
  - Dose reduction/cessation

Eczema

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors

- Treatment options:
  - Flare regimen:
    - Triamcinolone 0.1% BID (body)
    - Hydrocortisone 2.5% BID x 5 days (face, genital area)
    - Oral or systemic steroids
    - RTC: 2 weeks
  - Maintenance regimen:
    - Topical steroid BIW
    - Bland emollient daily

Psoriasiform dermatitis

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors

- Treatment options:
  - Flare regimen:
    - Triamcinolone 0.1% BID (body)
    - Hydrocortisone 2.5% BID x 5 days (face, genital area)
    - RTC: 2 weeks
    - Systemic retinoids
  - Maintenance regimen:
    - Topical steroid BIW
    - Bland emollient daily
### Erythema nodosum

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors

**Treatment options:**
- None if asymptomatic
- NSAIDs
- Oral prednisone (5 mg)

### Phototoxicity

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- RET inhibitors

**Treatment options:**
- Photoprotection
- Oral or topical steroids

### Xerosis

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- RET inhibitors

**Treatment options:**
- Bland emollient BID
- Bath BID
- Keratolytics (ammonium lactate or salicylic acid)
- Topical steroid PRN
### Keratosis pilaris-like eruption

- **EGFR inhibitors**
- **Multikinase inhibitors**
- **MEK inhibitors**
- **BRAF inhibitors**
- **HER2 inhibitors**
- **CTLA4 inhibitors**
- **PD-1 inhibitors**
- **mTOR inhibitors**
- **Bcr-Abl TKIs (2nd and 3rd gen)**

- **Treatment options:**
  - None
  - Topical retinoids
  - Topical keratolytic
  - Antihistamines if pruritic

### Scarring alopecia

- **EGFR inhibitors**
- **Multikinase inhibitors**
- **MEK inhibitors**
- **BRAF inhibitors**
- **HER2 inhibitors**
- **CTLA4 inhibitors**
- **PD-1 inhibitors**
- **mTOR inhibitors**
- **Bcr-Abl TKIs (2nd and 3rd gen)**

- **Treatment options:**
  - Pruritus: antihistamines
  - Topical/IL steroids
  - Dose reduction/cessation

### Bullous pemphigoid

- **EGFR inhibitors**
- **Multikinase inhibitors**
- **MEK inhibitors**
- **BRAF inhibitors**
- **HER2 inhibitors**
- **CTLA4 inhibitors**
- **PD-1 inhibitors**
- **mTOR inhibitors**
- **Bcr-Abl TKIs (2nd and 3rd gen)**

- **Treatment options:**
  - Topical/oral/IV steroids
  - Drug cessation
  - Long latency (3-16 weeks)
Vitiligo

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors

**Treatment options:**
- Nothing
- Topical steroids or topical tacrolimus +/- light therapy
- Possible association with PFS and tumor response

Pruritus

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- Bcr-Abl TKIs (2nd and 3rd gen)
- RET inhibitors

**Treatment options:**
- Determine etiology
  - Scabies
  - Drug reaction to beta blocker
  - Eczema
  - Lichen planus
  - Xerosis
  - Acneiform eruption
- Oral antihistamines
- Emollients
- Topical steroids
- Antidepressants/antipsychotics
- Phototherapy
- Dose reduction/cessation

Summary

- Dermatologic toxicities are significant
- Emerging field requiring well-described toxicities in clinical trials
- Overlap in drug toxicities
- Dermatologists are effective in managing symptoms
- Effect on ADLs heavily influences need for dose reduction/cessation of chemotherapy
  - Acneiform eruption
  - Hand foot skin reaction
  - Paronychia
References


References

References


Legend

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- VEGF inhibitors
- RET inhibitors
- Bcr-Abl TKIs (2nd and 3rd gen)
- Erlotinib, Gefitinib, Cetuximab
- Sorafenib, Sunitinib, Regorafenib
- Trametinib, Selumetinib
- Vemurafenib, Dabrafenib
- Lapatinib, Trastuzumab, Pertuzumab
- Ipilimumab
- Nivolumab, Pembrolizumab
- Sirolimus, Everolimus, Temsirolimus
- Pazopanib, Regorafenib
- Vandetanib
- Dasatinib,Nilotinib, Ponatinib