Chemotherapy and the Skin
Objectives:

• To define chemotherapy
• To define the common classes of drugs used and mechanism of action
• To identify dermatologic side effects of chemotherapeutic drugs
Chemotherapy

- Definition: the treatment of disease by a chemical agent; originally applied to chemicals that affect the causative organism unfavorably but do not harm the patient (Dorland’s Medical Dictionary)
- Common: medications used in the treatment of various cancers
Pharmacology

- **Cell cycle**
  - An ordered set of events that is necessary for cell growth and division
  - G₁: preparation
  - S: synthesis of DNA
  - G₂: preparation
  - M: mitosis
Pharmacology (cont.)

- Chemotherapy:
  - Goal is to target actively reproducing cells.
  - Combination therapies are chosen to attack different phases of the cell cycle.
  - Balance: the drugs do not affect only actively dividing CANCER cells, but also dividing normal cells.
Pharmacology- Agents

• Cell Cycle Specific:
  • Antimetabolites: affect DNA/RNA production in the S-phase
    • 5-FU, 6MP, cytarabine
    • methotrexate
  • Plant Alkaloids: affect tubule separation in the M-phase
    • vincristine, vinblastine
    • paclitaxel, etoposide
Pharmacology - Agents

- **Cell Cycle Non-Specific:**
  - Alkylating: interrupt proper DNA base-pairing
    - chlorambucil
    - cyclophosphamide, ifosfamide
    - thiotepa, busulfan
    - cisplatin, carboplatin
  - Antibiotics: bind to DNA
    - doxorubicin, daunorubicin (aka anthracyclines)
    - dactinomycin
    - bleomycin
Side Effects

- Mechanism of action
- Clinical presentation
- Classic agents
- Prevention
- Treatment
Side Effects

- Alopecia
- Stomatitis
- Hyperpigmentation
- Acral erythema
- Radiation recall
- Radiation enhancement
- Photosensitivity

- Extravasation
- Inflammation of keratoses
- Neutrophilic eccrine hidradenitis
- Eccrine squamous syringometaplasia
- Lymphocyte recovery
Anagen Effluvium

- **Mechanism:**
  - abrupt cessation of mitotic activity in the hair matrix cells

- **Clinical:**
  - Diffuse loss of hair loss seen as breakage in grooming
  - Day 7-10; most prominent 1-2 months
  - Scalp hair >> body hair
  - Not totally bald
    - Remember, not all hair is in active anagen
Anagen Effluvium
Anagen Effluvium (cont.)

- **Classic agents:**
  - Alkylating agents (e.g. cyclophosphamide, cisplatin)
  - Antimetabolites (e.g. 5FU, 6MP, methotrexate)

- **Prevention:**
  - Scalp hypothermia and tourniquets? Ineffective.
  - New research on p53 inhibition

- **Treatment:**
  - 2% minoxidil AFTER may help re-growth. Shown to speed re-growth by 50 days.
  - None: most people will regrow hair without difficulty.
    - Some grow back different texture/color
    - PERMANENT loss has been reported with busulfan and cyclophosphamide
Telogen Effluvium

- Patients may experience an additional telogen effluvium months following their therapy secondary to stresses of treatment, infections, fevers, etc...
Stomatitis

• **Mechanism:**
  - Direct: drug toxicity due to high mitotic rate
  - Indirect: BM suppression with secondary hemorrhage and infection

• **Clinical:**
  - Direct effects, day 7-10:
    - pain, burning, dryness
    - Erythema, edema, ulceration; rarely vesiculation
  - Indirect effects, day 14 BM:
    - Fever and pain with oral lesions; FEW signs of inflammation
      - Bacterial oral flora, most common
      - Candida (thrush)
      - HSV
Stomatitis (cont.)

- **Classic agents:**
  - Antimetabolites (e.g. 5FU, 6MP, mtx)
  - Antibiotics (e.g. doxorubicin, dactinomycin)

- **Prevention:**
  - Oral hygiene (brush, floss, rinse with sodium bicarbonate)
  - Ice chips during therapy
  - Oral glutamine, sucralfate

- **Treatment:**
  - Supportive
    - Coating agents (kaopectate, MOM)
    - Anesthetic agents (benzocaine, viscous lidocaine)
    - PO pain meds (acetaminophen, codeine)
  - Culture for infection. Low threshold to treat.
Mucositis from chemotherapy
Hyperpigmentation

- One of the most common side effects; may affect skin, hair, nails, or mucosa
- Mechanism: varies
  - Increased blood flow with drug deposition
  - Endocrine mediated
  - Depletion of tyrosinase inhibitors
- Clinical: variable
  - Localized or diffuse
  - Under occlusive dressings
Hyperpigmentation (cont.)

- **Classic agents:**
  - “flag sign” of hair
    - methotrexate
  - “flagellate”: often on trunk
    - bleomycin
  - “serpentine”: overlying the vein of infusion
    - fluorouracil
  - occlusive dressing
    - thiotepa
    - BCNU, ifosfamide
Hyperpigmentation (cont.)

- **Nail pigmentation**
  - Brown banding: daunorubicin
  - White banding: cyclophosphamide
  - General hypermelanosis: 5FU, hydroxyurea

- **Generalized hyperpigmentation**
  - “Busulfan Tan” (spares palms)

- **Pigment on gingiva**
  - cyclophosphamide
  - Busulfan
Flagellate hyperpigmentation with bleomycin
Acral Erythema

- A.k.a. hand-foot syndrome, erythrodysesthesia, Burgdorf’s
- Mechanism:
  - Direct toxic effect, accumulating in acral sites
  - Self-limited variant of GVHD
- Clinical:
  - Prodrome of dysesthesia
  - 2-4 days later: pain, edema, well-demarcated erythema beginning on lateral borders
  - Significant desquamation
  - Hands > feet
  - Bullous variant (cytarabine, methotrexate)
  - Hyperpigmentation and PPK in black patients
Acral Erythema
Acral Erythema (cont.)

- Classic Agents: “A, B, C, D, et F”
  - A: acral erythema or...
  - B: “Burgdorf’s Syndrome”
  - C: cytarabine
  - D: doxorubicin (liposomal especially!)
  - Et
  - F: fluorouracil
Acral Erythema (cont.)

- **Prevention:**
  - Decrease dose of medicine
  - Decrease time of contact
  - Cool extremities during treatment

- **Treatment:**
  - Make the diagnosis
    - Can be confused with GVHD, and can occur in the same patient.
    - Serial biopsies
  - Stop medicine
  - Pyridoxine (B6) supplementation
  - Elevation cool compresses, wound care
Radiation Effects

- Recall:
  - Therapeutic irradiation
  - UV light exposure

- Current:
  - Enhancement of irradiation
  - Photosensitivity
Radiation Recall

- **Mechanism:**
  - DNA repair defect
  - Altered microvasculature

- **Clinical:**
  - Inflammatory reaction at exact site of prior radiation; erythema, edema, +/- vesiculation
  - Reaction seen hours to days after drug administration
    - Radiation occurred 8 days-15 YEARS prior!
Radiation Recall (cont.)

- **Classic Agents:**
  - doxorubicin
  - dactinomycin

- **Prevention:**
  - increase time between treatments
  - Decrease the initial radiation dose

- **Treatment:**
  - Clears spontaneously with cessation of drug
  - Symptomatic; may benefit from short course of systemic steroids
UV Recall

- **Mechanism:**
  - Actinically damaged skin may have more fragile vascular tissue

- **Clinical:**
  - Enhancement of former sunburn site
  - Sunburn must have occurred between 1-5 days prior to drug administration
  - Reaction will subside gradually despite continued treatment
UV Recall (cont.)

- Classic Agents:
  - Methotrexate!!!
  - Suramin
  - Taxanes (e.g. paclitaxel)

- Treatment:
  - Symptomatic
  - Leucovorin is no help
Radiation Enhancement

• Mechanism:
  • Synergy of radiation and chemo side effects
    • increased blood supply
    • increased percentage of cells in S-phase
    • interference with repair enzymes

• Clinical:
  • BAD radiation dermatitis: erythema, edema, vesiculation, ulceration
  • Drug and radiation occur within 7 days of each other
Radiation Enhancement

Acute ulceration

Chronic fibrosis
Radiation Enhancement (cont.)

- Classic Agents:
  - cyclophosphamide combos
  - dactinomycin
  - doxorubicin
  - 5-FU
- Prevention:
  - Decrease the drug dose if radiation expected
- Treatment:
  - Self limiting reaction; local wound care only
  - May have long term sequelae of atrophy or fibrosis
Photosensitivity

- **Mechanism:**
  - photoTOXIC reaction

- **Clinical:**
  - Exaggerated sunburn; erythema, edema, pain, stinging, tenderness
  - Face, V-of-neck, dorsum of hands
  - Photo-onycholysis of finger nails
Photosensitivity (cont.)

- **Classic agents:**
  - dacarbazine
  - 5-FU
  - vinblastine
  - flutamide: thought to be photoALLERGIC

- **Prevention:**
  - Sun precautions counseling

- **Treatment:**
  - Sunscreens, protective clothing
Inflammation of Keratoses

- **Mechanism:**
  - Increased abnormal DNA in these lesions
  - Form of “radiation recall”

- **Clinical:**
  - Inflammatory, pruritic, hyperkeratotic papules
  - Apparent within 1 week of starting drug
  - May actually make lesions regress
Inflammation of Keratoses (cont.)

- Classic agents:
  - Systemic 5-FU
  - cytarabine, fludarabine
  - dactinomycin, doxorubicin (like recall)

- Treatment:
  - None; the inflammation may actually be beneficial
  - Symptomatic treatment with topical steroid
Neutrophilic Eccrine Hidradenitis

- **Mechanism:**
  - Direct toxic effect: concentration of drug in the sweat glands
- **Clinical:** (in classic, chemo-associated)
  - Nonspecific “fever and a rash”
  - Erythematous/violaceous macules, papules, or plaques
  - Asymptomatic or tender
  - Rash after 2 days-3 weeks of drug
NEH (cont.)

- **Classic Agents:**
  - cytarabine
  - cyclophosphamide
  - doxorubicin
  - bleomycin

- **Prevention:**
  - 60% of patients have recurrence
  - Dapsone, NSAIDS

- **Treatment:**
  - Need to make diagnosis; get biopsy
  - No therapy needed, self-limited
NEH (cont.)

- **Histopathology:**
  - Dense neutrophilic infiltrate in and around eccrine units
  - Necrosis of eccrine epithelial cells
Eccrine Squamous Syringometaplasia

- **Mechanism:**
  - Concentration of drug in sweat glands
  - Non-inflammatory *spectrum* of NEH
  - These conditions may be primary sweat gland processes?

- **Clinical:**
  - Nonspecific rash, similar to NEH
  - Begins 2-39 days after starting therapy
Eccrine Squamous Syringometaplasia

- **Classic Agents:**
  - None; caused by virtually any chemotherapeutic

- **Treatment:**
  - None
  - Make the diagnosis with biopsy
Lymphocyte Recovery

- **Mechanism:**
  - In BMT patients, return of the few immunocompetent lymphocytes to the circulation

- **Clinical:**
  - Day 6-21 of BMT ablation therapy
  - Erythematous macular/papular rash that becomes confluent; may be erythrodermic
  - Fever for first 2-3 days; cultures negative
  - Desquamation with defervescence
Lymphocyte Recovery (cont.)

- Classic Agents:
  - None in particular
  - cytarabine, daunorubicin, cyclophosphamide, etoposide, vincristine
- Treatment: ???
Extravasation

- **Mechanism:**
  - Direct infiltration of agent into surrounding tissues
  - Vesicant: toxic injury
  - Irritant: inflammatory reaction

- **Clinical:**
  - Vesicant:
    - Early: mild erythema and slight “tingling”
    - Late: necrosis, eschar, ulceration
  - Irritant: aching, tightness, phlebitis
Extravasation (cont.)

- **Classic Agents:**
  - Most drugs can do this. Most can be both irritant or vesicant!
  - Vesicant: antibiotics (doxorubicin, daunorubicin, dactinomycin)
  - Irritant: doxorubicin, daunorubicin

- **Prevention:**
  - Procedural accuracy!

- **Treatment:**
  - Stop infusion immediately
  - Surgical consult
  - Elevation and cold packs
    - EXCEPT vinca alkaloids...HOT packs only!
Extravasation (cont.)

• Treatment Antidotes:
  • dox/daunorubicin, mitomycin = DMSO
  • vinca alkaloids, etoposide = hyaluronidase
  • dacarbazine, cisplatin, mechlorethamine = sodium thiosulfate
• Do NOT use local steroid injection or sodium bicarbonate
Miscellaneous Reactions:

- Folliculitis = dactinomycin
- Flushing = any!
- Sclerodermoid = bleomycin, docetaxel
- Raynauds = bleomycin
- Leg Ulcers = hydroxyurea
- Dermatomyositis = hydroxyurea
- Pulmonary fibrosis = bleomycin, methotrexate
- Hypersensitivity = L-asparaginase
- Sweet’s = GCSF
Other reactions