

Chemotherapy and the Skin

Objectives:

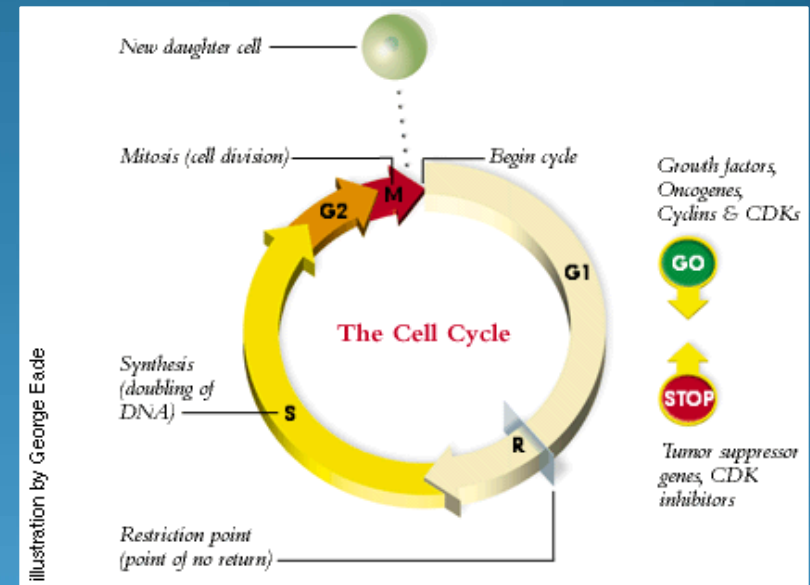
- To define chemotherapy
- To define the common classes of drugs used and mechanism of action
- To identify dermatologic side effects of chemotherapeutic drugs

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 that 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 (eg. cyclophosphamide, cisplatin)
- Antimetabolites (e.g. 5FU, 6MP, methotrexate)

- Prevention:

- Scalp hypothermia and tourniquetes? 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

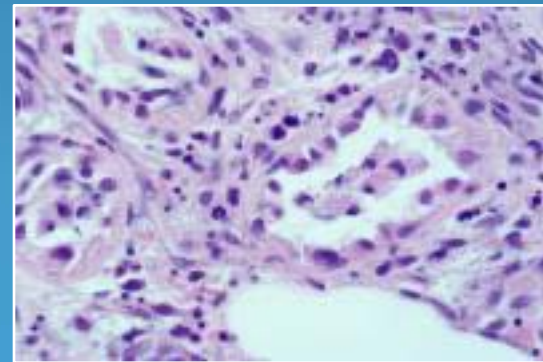
- Mechanism:
 - Direct toxic effect: concentration of drug in the sweat glands
- Clinical: (in classic, chemo-associated)
 - Nonspecific “fever and a rash”
 - Erythematous/violaceous macules, papules, or plaques
 - Asymptomatic or tender
 - Rash after 2 days-3 weeks of drug

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

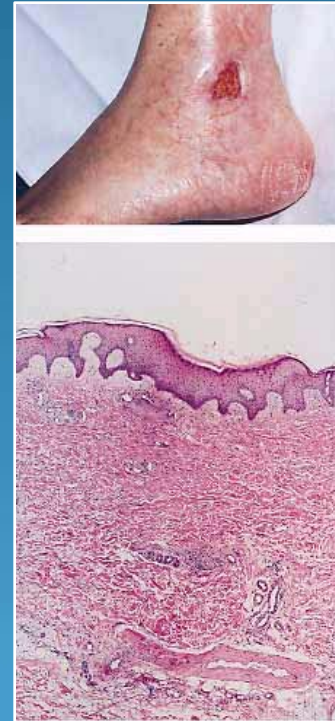
Miscellaneous Reactions:

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

Hydroxyurea



Dermatomyositis



Leg ulcer

Other reactions

