CHEMOTHERAPY AND RADIOTHERAPY EFFECTS ON THE SKIN

Prepared by: Charlene DeHaven, MD, FACEP, Clinical Director

Both chemotherapy and radiation therapy commonly have side effects that involve the skin. Some of these are broad effects from the treatments in general and some are specific to certain chemotherapeutic drugs used. Patients may be allergic to any medication, including chemotherapy. Allergic skin manifestations include general allergic rashes from medications, fixed drug eruptions and contact allergies. However, this discussion will be restricted to those skin effects unique to chemotherapy and radiation therapy.

Cancers are composed of abnormal cells that divide rapidly. The faster the tumor's growth rate the more rapidly its cells are multiplying. Although a more rapid rate of cellular division is associated with greater malignant potential, this rapid growth rate also makes the tumor susceptible to chemotherapeutic drugs. Chemotherapy targets cells that are rapidly dividing. The goal of chemotherapy is to kill as many cancer cells as possible so the tumor can either be completely eradicated, i.e. "cured", or placed in remission, a state where there still may be some cancer cells present in the body but the patient is without symptoms and feels well for an extended period of time.

In addition to tumor cells, there are certain normal cells in the body which are also rapidly dividing. Chemotherapeutic drugs target all rapidly-dividing cells and therefore affect not only tumor cells but also any other cells in the body which are undergoing rapid cell division. Other normal rapidly dividing cells include skin and the skin's appendages hair and nails, gastrointestinal cells, bone marrow and its product blood cells, and reproductive cells including sperm and ova. Oral and vaginal mucosa are also epithelial cells and are part of the skin. It makes sense that skin effects are commonly seen with chemotherapy since both skin cells and tumor cells are undergoing rapid cell division. The patient may notice a temporary decrease in appearance of wrinkling but as skin thins secondary to chemotherapy overall increased fragility results. Decreased functionality of the lipid barrier of the stratum corneum may be related to increased sensitivity. Other common side effects of chemotherapy involve other cells of epithelial origin and include ulcers and infections in the mouth, stomach and intestine. Toxicity to other rapidly dividing cells causes anemia, decreases in white blood cells and platelets and temporary loss of reproductive ability. As long as a few of the body's normal cells in skin, GI tract, reproductive tract and bone marrow remain the body can regenerate and recover these functions once the chemotherapy is stopped and sufficient time is allowed for recovery.

Extravasation injury is a type of skin injury that occurs when a chemotherapy drug given intravenously leaks out of the vein and into the skin. Depending on the drug in question, this effect can be mild swelling, local irritation and inflammation or even actual tissue necrosis. Extravasation injury may occur with drugs other than chemotherapy but is often more severe with chemotherapeutic agents as they tend to be more damaging to tissues.

Alopecia is hair loss that with chemotherapy is associated with toxicity to rapidly dividing hair cells. This includes all body hair and is not limited to scalp hair only. Recovery occurs and hair growth resumes after chemotherapy stops although there may be an alteration in hair color, texture or curl.

Certain drugs can cause specific types of allergic or hypersensitivity responses. The platinum derivatives (cisplatin, carboplatin) can cause an IgE-mediated hypersensitivity with itching, redness and swelling occurring within an hour after the infusion is begun. If life-threatening this reaction is termed "anaphylaxis"and the drug will not be given again in these severe cases. Formation of antigen-antibody complexes occurs with methotrexate which causes a vasculitis (inflammation surrounding blood vessels) or rituximab can cause serum sickness (an illness with flu-like symptoms). A specific type of rash called

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"erythema multiforme" of which the hallmark is the "target lesion" is caused by antigen-antibody complexes and can occur with a number of medicines including chemotherapeutic agents. Activated T cells cause contact allergy and may be seen with nitrogen mustard (mechlorethamine).

The increased incidence of infections during cancer treatment is related to a number of factors. One of these is simple physical disruption of the epithelial barrier on a cellular level. Stomatitis refers to ulcerations in the mouth involving buccal mucosa (cheeks) or tongue. When the normal barrier of the mucosa is disrupted there is impaired ability to protect against infections. Mucous-producing cells are also damaged which strips away another barrier to infection. Yeast infections with Candida are especially common both in the mouth and throughout the interior of the GI tract. A similar mechanism damages epithelial cells of the vaginal mucosa causing yeast infections, decreased mucous production and dryness. Radiation treatments are also toxic to the rapidly dividing cells of the skin. Since the skin is a continuous organ, radiation at one site can affect skin in other areas. Thus, mouth or vaginal dryness can be associated with radiation therapy given at sites remote to these locations. Infections can be local (involving skin and GI tract) or the damaged skin barrier can serve as an entry portal for organisms traveling to other organs and causing infections at these remote sites. Sepsis (a pervasive infection disseminated via the bloodstream) is a common infectious complication of cancer and its treatment. Sepsis can arise from any number of possible sites. One such site is the damaged skin barrier which may allow entry of organisms into the blood stream.

Decreasing immune function also confers impaired ability to deal with infectious challenges. The skin functions not only as a physical barrier to the environment but also as a barrier with immune ability. Langerhans cells function in primary skin immunity and are the mast cells of the skin. Resistance and immunity decline in general during cancer treatment as secondary effects of chemotherapy and radiation therapy impact the rapidly-dividing population of immune cells. This is yet another contributing factor to the higher incidence of infections of all sorts associated with cancer and its treatment.

Pigmentary changes can involve the skin, mucous membranes or nails. These may be temporary or permanent. Following alopecia, hair may regrow with a color or texture change. Pigmentary changes are particularly common with the cytotoxic drugs such as alkylating agents or tumor-directed antibiotics. Hyperpigmentation of the gums can be found with cyclophosphamide treatment and is permanent. 5-fluorouracil (5-FU) treatment is often seen with hyperpigmentation reactions either diffusely or in only sun-exposed areas. Pigment changes with 5-FU can also follow the pattern of an underlying vein and appear twisting or serpentine. 5-FU can darken the mucosa of the tongue, conjunctiva of the eyes or nails. Tegafur, a 5-FU analog, can cause circular areas of pigmentation of the palms, soles and nails. Additional drugs may result in generalized hyperpigmentation. These include busulfan (referred to as the "busulfan tan"), pegylated liposomal doxorubicin, hydroxyurea and methotrexate. Daunorubicin can cause hyperpigmentation in solar-exposed areas. Increased pigmentation in areas of injury or pressure may be seen with cisplatin, hydroxyurea and bleomycin. Some drugs are secreted in sweat and can cause hyperpigmentation under adhesive tape; these include docetaxel, thiotepa and ifosfamide. Circular areas of scalp hyperpigmentation can be associated with daunorubicin.

An acneiform rash can be seen with the epidermal growth factor receptor inhibitors such as cetuximab and gefitinib. These papules and pustules look like acne although the typical comedone of acne is not found. Patients receiving the EGF receptor inhibitors commonly have some of these acneiform lesions although it is severe in only a small number of patients. Treatment with the tetracycline-type antibiotics may initially be helpful although the lesions tend to recur as chemotherapy

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continues. Although some acneiform lesions are common in most patients receiving this group of drugs, it is severe in a minority of patients and rarely results in discontinuation of the chemotherapy.

Rashes are also common with the tyrosine kinase signal transduction inhibitors such as imatinib. Some type of rash occurs in as many as 90% of patients on the higher doses.

Beau's lines are transverse lines seen in nails. Beau's lines can be seen with chemotherapy or other critical illness. The cycles of chemotherapy correspond to the width of the lines in the nail. Many chemotherapy drugs can cause pigmentary changes, bands or lines in the nails.

Oncholysis refers to a lifting up of the nail from the nail bed. It is most commonly seen with paclitaxel and docetaxel but also with cyclophosphamide, doxorubicin, 5-FU, hydroxyurea and the combination of bleomycin plus vinblastine.

Inflammatory changes around the nail even leading to paronychia (an infection adjacent to the nail) can be seen with EGF inhibitors such as gefitinib and cetuximab. The taxanes (paclitaxel, docetaxel) can also be associated with paronychia.

Acral erythema or hand-foot syndrome is an erythema of palms and/or soles that can be associated with chemotherapy. It can be quite painful and can even result in blistering and sloughing of skin. It may respond to decreasing the dose of the agent.

Photosensitivity can be seen with many chemotherapy drugs. A phototoxic reaction is a type of allergic response seen on sun exposure and consists of edema, redness, pain and tenderness in solar-exposed areas. Phototoxic reactions may ultimately result in permanent hyperpigmentation as they are associated with blistering and severe skin damage. Methotrexate can cause a photoenhancement in which giving the drug several days after sunburn causes the sunburn to reappear.

In patients with autoimmune disorders such as scleroderma or lupus, administration of a chemotherapy agent can result in the appearance of a circular red scaly rash. This is related to the drug but also involves the autoimmune process itself.

Radiation therapy also often results in dramatic changes in the skin. These depend on the total dose, size of the port (area over which the radiation is administered), depth of penetration (i.e. how close to skin). Changes of radiation dermatitis may be acute or chronic. Acute changes consist of erythema, irritation, pain or local dermal swelling. Chronic radiation dermatitis can result in scarring, thinning of the skin, telangiectasias, increased sensitivity to other agents or environmental insults. The pathogenesis of radiation dermatitis is free radical damage to cells of the skin. Therapeutic effects of radiation therapy are also on a free radical mechanism. With radiation therapy for carcinoma of the breast, the severity of radiation dermatitis tends to increase with breast size greater than a D cup; this may relate to overall port size required. Considering all patients who receive radiation therapy for carcinoma of the breast, as many as 90% may experience some degree of radiation dermatitis.

Radiation recall dermatitis occurs in a previously irradiated area of skin that develops marked inflammation after chemotherapy is given. Radiation recall dermatitis has been described with dactinomycin. It is more likely with higher doses of chemotherapy and usually occurs with the first dose. IV chemotherapy is more likely to cause this than oral medicines perhaps because IV doses result in

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more rapid and higher blood levels. However, the radiation recall dermatitis from oral agents tends to last longer than that from IV chemotherapy. It has been described in association with tamoxiphen.

Radiation sensitization (also termed radiation enhancement) occurs in the radiation therapy field and within 1-2 weeks after the chemotherapy is given. The skin changes appear the same as that for radiation recall dermatitis and consist of redness, edema, superficial sloughing of skin and superficial ulcerations.

Considerable emphasis should also be given to the pronounced effects caused on the psyche through physical effects in the skin from chemotherapy and radiation therapy. The diagnosis and treatment of cancer often corresponds with one of the most difficult times in the patient's life. Since the patient's external appearance is determined in large part by their skin, any deterioration in their skin as perceived by the patient can worsen depression and self-concept, leading to the exacerbation of emotional difficulties. Furthermore, the occurrence of depression has been clearly linked to accompanying decreases in immunity. Improving self-concept by treating skin effects associated with cancer treatment can lift depression. This improves immune response and increases resistance to all types of disease particularly infections and the cancer itself. The impact of these skin changes should not be minimized and every effort should be made to assist the patient in this regard, both with understanding of the processes involved as well as their treatment.

SKIN REACTIONS IN CHEMOTHERAPY & RADIATION THERAPY

SKIN REACTIONS FOUND WITH CHEMOTHERAPY	GENERAL CLASS OF REACTION	DRUG CLASS OR NAME
Extravasation injury (CTx agent leaks into surrounding tissue)	Varying severity depending on specific drug swelling, redness, irritation, local tissue loss (necrosis)	most CTx drugs
Toxicity to rapidly dividing cells	Alopecia, mouth ulcers, GI tract ulcers, GI yeast overgrowth, tract overgrowth(yeast) & other infections from decreased mucous production(mucous is protective), bone marrow effects of anemia, decreased platelets, decreased WBCs, decreased production of sperm & ova	most CTx drugs, probability of occurrence depends on how much the drug effects rapidly dividing cell groups
Allergic or immune complex reactions		
IgE mediated	Itching, redness, swelling within 1 hr after infusion begun (if life-threatening is termed "anaphylaxis" and includes decreased blood pressure, decreased level of consciousness, airway and breathing compromise)	Platinum derivatives (cisplatin, carboplatin)
Vasculitis (from antigen-antibody complexes)	Generalized vascular inflammation with end-organ damage	Methotrexate
Serum sickness (antigen-antibody complexes)	Flu-like symptoms which can progress to life-threatening	Rituximab
Erythema multiforme (antigen-antibody complexes)	Rash with typical "target lesions" involving extremities including palms and soles, can progress to generalized	Many CTx agents
Contact allergy (activated T-cells)	Allergic response where drug touches skin (erythema, local swelling, desquamation, blistering, necrosis possible)	Nitrogen mustard (mechlorethamine)
Activation of already-existing immune complex reaction in collagen vascular diseases of SLE (lupus) and PSS (scleroderma)	CTx drug activates immune complexes already circulating due to underlying collagen vascular disease process-circular causing circular red scaly rash	Numerous CTx drugs
Pigment changes of skin, mucous membranes or nails		
Variety of pigmentary changes of skin and appendages	These general types pigmentary changes especially common with drugs in column to right	Various cytotoxic drugs (alkylating agents, tumor-directed antibiotics)
Gums	Permanent hyperpigmentation of gums	Cyclophosphamide
Various types of hyperpigmentation	Generalized hyperpigmentation (all skin), of sun-exposed areas only, serpentine (follows underlying vein where drug infused), mucosa of tongue, nails, conjunctiva of eyes	5-Fluorouracil (5-FU)
Hyperpigmentation of palms, soles, nails	Circular areas of hyperpigmentation in these locations	Tegafur (5-FU derivative)
Generalized hyperpigmentation of all skin	All skin involved	Busulfan (termed "busulfan tan") usulfan tan"), pegylated liposomal doxorubicin, hydroxyurea, methotrexate

SKIN REACTIONS FOUND WITH CHEMOTHERAPY	GENERAL CLASS OF REACTION	DRUG CLASS OR NAME
(...continued)		
Hyperpigmentation of solar-exposed skin	Sun-exposed areas only	Daunorubicin
Hyperpigmentation in areas of pressure or injury	Injured skin only although inciting injury may be mild	Cisplatin, hydroxyurea, bleomycin
Drug secreted in sweat may induce pigmentation	Under areas where adhesive tape applied and skin sweats	Docetaxel, thiotepa, ifosfamide
Scalp hyperpigmentation	Circular hyperpigmented areas in scalp	Daunorubicin
Rashes		
Generalized rash of hands and feet	Usually localized but can become more generalized	Tyrosine kinase signal transduction inhibitors (occurs with 50% of patients of higher doses of imatinib)
Acneiform rash	Papules and pustules similar to acne although this rash contains NO comedones, commonly involves face and also back, upper chest	EGFR (epidermal growth factor receptor) inhibitors (cetuximab, efitinib)
Acral erythema "hand-foot syndrome"	Erythema of hands and feet	Various chemotherapy drugs
Nail changes		
Beau's lines	Transverse lines in nails ails, bands correspond to when drug was given or time when critical illness occurs	Any chemotherapy agent or critical illness
Oncholysis	Nail lifts up from base	Paclitaxel, docetaxel, cyclophosph-amide, doxorubicin, 5-FU, hydroxyurea, combination of vinblastine+bleomycin
Nail inflammation	Inflammatory changes around nail including paronychia	EGFR (epidermal growth factor receptor) inhibitors (cetuximab, gefitinib), taxanes (docetaxel)
Light-related reactions		
Photo-enhancement	Drug given several days after a sunburn causes sunburn to re-appear in that area	Many drugs
Photosensitivity	Patient more sensitive to sun in solar-exposed areas and may develop severe sunburn	Many drugs
Phototoxicity	Allergic response on solar-exposed areas may be severe with edema, erythema, severe pain, blistering--if ering severe can result in permanent hyperpigmentation	Many drugs

SKIN REACTIONS IN CHEMOTHERAPY & RADIATION THERAPY IN COMBINATION

SKIN REACTIONS FOUND WITH CHEMOTHERAPY	GENERAL CLASS OF REACTION	DRUG CLASS OR NAME
Radiation recall dermatitis	Previously irradiated area develops severe inflammation which can result in necrosis (skin sloughing) and scarring	Tamoxiphen, dactinomycin (usually occurs with first dose of CTx or with higher doses, usually occurs with IV CTx rather than oral)
Radiation enhancement–also termed Radiation sensitization dermatitis	Occurs in previously irradiated skin within 1-2 weeks post-CTx with erythema, edema, superficial ulcerations, superficial skin sloughing	Multiple CTx drugs

SKIN REACTIONS IN RADIATION THERAPY ALONE

Acute radiation dermatitis	Immediate dermatitis occurring in radiated areas with erythema, pain, dermal swelling, itching	Can occur with all radiation therapy Mechanism is free radical damage to tissue
Chronic radiation dermatitis	Long-term effects of radiation therapy in port area with thinning of skin, scarring and contractures, telangiectasias, long-term skin sensitivity to irritants & environmental agents	Can occur with all radiation therapy Mechanism is free radical damage to tissue Severity depends on port size and total dose

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