DermNet NZ

Authoritative facts about the skin from the New Zealand Dermatological Society Incorporated.

Skin toxicity of chemotherapy drugs

Why is it important to know about chemotherapy drugs and the skin?

Each year, 10.9 million people worldwide are diagnosed with cancer and this incidence is rising. This increase reflects the world's growing population and the fact that people are living longer. Chemotherapy is a crucial component to all cancer management and with this rising cancer burden, doctors and patients alike will see an increasing incidence of chemotherapy-related skin toxicity.

What are the skin rashes associated with chemotherapy?

- Acral erythema
- Alopecia (hair loss)
- Photosensitivity (increased sensitivity to sunlight)
- Recall reactions
- Acneiform (pimple-like) eruptions
- Skin necrosis
- Neutrophilic eccrine hidradenitis
- Ecrine squamous metaplasia
- Hyperpigmentation
- Nail changes
- Mucositis
- Sclerotic dermal reactions
- Vascular injury
- Other allergic and non-allergic drug reactions

Acral erythema

Acral erythema is also known as palmoplantar erythrodysesthesia or hand-foot syndrome. It manifests as painful erythema (redness of the skin) of the hand and foot, with or without bullae (large blisters). These symptoms can be preceded by dysasthesia (altered sensation of the skin). The pain from this rash may be so severe that daily activities are limited.

If recognised early, the usual course of acral erythema is desquamation (shedding of the outer layers of the skin) followed by re-epithelialization (re-growth of the outer layers of the skin).

The exact mechanism is unknown, but it is postulated that the skin of the hands and feet favour a higher level of certain chemotherapy drugs which causes direct toxicity to the skin cells.

Which drugs are responsible?

The most commonly associated drugs are:

- Cytarabine
- Docetaxel

- Doxorubicin
- Fluorouracil.

Management

Often stopping or reducing the dose of the chemotherapy drug will result in regression of acral erythema. Supportive care may include wound dressings, analgesia (pain relief) and cold compresses.

Alopecia

Alopecia (hair loss) is the most common side effect of cancer treatment and often is the most distressing to the patient's self-image. It occurs 7-10 days after treatment and continues to progress over 2-3 months.

There are two main ways chemotherapy drugs cause alopecia:

- Anagen effluvium (most common) – refers to toxic effects on rapidly dividing hair cells
- Telogen effluvium – refers to increased shedding of normal hair cells

Alopecia is often temporary and resolves after treatment is stopped but some chemotherapy drugs such as busulphan and cyclophosphamide can cause permanent hair loss.

Which drugs are responsible?

Most chemotherapy drugs cause alopecia but the most common culprits are the following:

- Taxanes (e.g. paclitaxel and docetaxel)
- Anthracyclines (e.g. doxorubicin, idarubicin, epirubicin and mitoxantrone).

Management

Several strategies have been tried to reduce alopecia such as:

- Cooling the scalp to 24°C
- Using a headband to reduce the amount of chemotherapy drug delivered to the scalp
- Immune treatment to upregulate cytokines (hormone like proteins secreted by cells)

Unfortunately none have consistently been shown to be effective. It is important to advise patients of this potential side effect and to provide a wig.

Photosensitivity

Certain chemotherapy drugs result in photosensitivity (increased sensitivity to sunlight) causing sunburn with minimal sun exposure.

Which drugs are responsible?

The chemotherapy drugs which most commonly cause this are:

- Methotrexate
- Fluorouracil
- Dacarbazine.

Management

Patients should be advised of this potential side effect and to protect themselves from the sun. This involves the use of sunscreen and protective clothing.

Recall reactions

The term " recall reaction " refers to erythema (redness of the skin) in areas of previously quiescent sunburn or

radiotherapy. The exposure to the sun or radiotherapy may have been weeks to months ago and the skin may have fully recovered until the patient was given chemotherapy.

The actual mechanism is not fully understood but it has been postulated to occur as a result of the recovering keratinocytes (skin cells) being damaged by the chemotherapy drugs, as these cells are the ones which are most rapidly dividing and regenerating.

Which drugs are responsible?

The most common drugs which can cause this are:

- Gemcitabine
- Methotrexate
- Docetaxel
- Etoposide
- Doxorubicin.

Management

Treatment involves minimising exposure to the sun, good wound care. There is possibly a role for topical steroid creams to reduce the inflammation.

Acneiform ("pimple-like") eruptions

Also known as folliculitis, an acneiform reaction begins as facial erythema followed by papules (small bumps) and pustules (small pockets of pus) over the face and upper trunk. Unlike true acne, the pustules are sterile (they contain no bacteria).

Which drugs are responsible?

Actinomycin D is the most common cause. Other drugs may also cause folliculitis, particularly the epidermal growth factor receptor (EGFR) inhibitors such as gefitinib and cetuximab.

Management

Oral tetracycline antibiotics (e.g. doxycycline) and topical antibiotics can help. Even though bacteria do not appear to be involved in the acneiform eruptions, these antibiotics have an anti-inflammatory effect over and above their anti-bacterial properties. Topical retinoids and benzoyl peroxide may also help.

Skin necrosis

Skin necrosis is the term used to describe dead skin cells, which blacken and peel off. Most chemotherapy drugs are toxic when exposed to the skin. Drugs that are meant to be delivered into veins and arteries may leak into the subcutaneous tissue (extravasation).

There are two types of skin necrosis reaction:

- Irritants – The chemotherapy agent causes a phlebitis (inflammation of veins) and chemical cellulitis (inflammation of the deeper layers of the skin).
- Vesicants or blistering agents – The chemotherapy agent causes severe tissue necrosis (death of cells), resulting in ulcers and eventual scar formation.

Which drugs are responsible?

Most chemotherapy drugs are irritants if they extravasate. Doxorubicin is the most vesicant and can cause necrosis, ulceration and thrombosis (blood clots).

Management

Local wound care and the use of cold packs or heat packs can help with wound healing. When vesicants like doxorubicin leak into the skin, early plastic surgical advice may be required due to the expected death of

extensive areas of skin.

Neutrophilic eccrine hidradenitis

Neutrophilic eccrine hidradenitis is characterised by tender red papules, plaques or nodules on the trunk, face and ears. The diagnosis of this condition relies on skin biopsy and analysing the histological (microscopic) changes. Neutrophils (a type of white cell) are seen surrounding eccrine (sweat) glands.

The cause is thought to be the high concentrations of chemotherapy drugs secreted into the sweat glands.

Which drugs are responsible?

The most commonly implicated agents are:

- Cytarabine
- Bleomycin.

Management

Neutrophilic eccrine hidradenitis often heals without treatment within days to weeks. Appropriate management involves performing a skin biopsy to help establish the diagnosis. Supportive treatment such as systemic steroids, non-steroidal analgesics and dapsone helps to shorten the duration of the rash and relieve pain.

Eccrine squamous metaplasia

Eccrine squamous metaplasia is a rare kin reaction. It presents as a non-specific red papular, crusted eruption that can be confused with squamous cell carcinoma. It is closely related to neutrophilic eccrine hidradenitis.

Which drugs are responsible?

Three large groups of chemotherapy drugs have been known to cause this skin reaction.

- Nitrogen mustards e.g. cyclophosphamide, chlorambucil and melphalan
- Anthracyclines e.g. doxorubicin, idarubicin and epirubicin.
- Antimetabolites e.g. azathioprine, methotrexate, fluorouracil and capecitabine

Management

The treatment of eccrine squamous metaplasia is similar to that for neutrophilic eccine hidradenitis. Spontaneous resolution generally occurs.

Hyperpigmentation (excess darkening of the skin)

The most unique pattern of hyperpigmentation is the flagellate hyperpigmentation caused by bleomycin. This reaction occurs as dark brown linear streaks about 10cm in length and criss-crossing one another in a pattern resembling a flagella (whip-like structure of certain bacteria that assists them in moving).

Various mechanisms have been reported to explain the cause of this hyperpigmentation. The most well accepted hypothesis is that bleomycin induces pruritus (itching) of the trunk causing the patient to scratch. The action of scratching causes increased leakage of bleomycin into the skin.

What other drugs can cause hyperpigmentation?

Fluorouracil, vinorelbine and daunorubicin can cause hyperpigmentation of the skin, nails and oral mucosa. Although not characteristically flagellate in nature, pigmentation caused by these agents can follow the distribution of veins (called serpentine supravenous hyperpigmentation) or may simply be patchy and macular (flat nonspecific colour change).

Management

Oral antihistamines may be helpful if there is marked itching. Topical bleaching agents such as hydroquinone can

decrease melanin production and assist in clearing of areas of pigmentation. However, when the chemotherapy drug is stopped, the pigmentation may be expected to slowly disappear without treatment.

Nail changes

There are several changes that can occur in the nail (nail diseases). This is due to direct toxicity of the chemotherapy drug to the nail plate.

- Beau's line – a transverse groove in the nail plate
- Oncholysis – separation of the nail plate from the underlying nail bed
- Onchomadesis – loss of the entire nail
- Nail pain, thickening and/or thinning
- Hyper- or hypo-pigmentation – pale or dark streaks in the nail plate

Which drugs are responsible?

Two groups of chemotherapy drugs are particularly prone to cause nail changes:

- Taxanes e.g. docetaxel and paclitaxel
- Anthracyclines e.g. doxorubicin, idarubicin and epirubicin.

Nail changes may also be seen with hydroxyurea.

Management

Often nail changes disappear when the damaged nail is replaced by the growth of new nails. The optimal management may need to include pain killers as some of these nail changes can be exquisitely painful.

Mucositis

Mucositis refers to inflammation of mucosal surfaces. The lining of the mouth and the gastrointestinal tract are extremely susceptible to being damaged by chemotherapy drugs due to high cell regeneration and growth rate. Up to 80% of chemotherapy patients suffer from this complication.

The symptoms begin with burning and erythema of the mouth followed by erosions and ulcerations that are intensely painful. Although the signs in the mouth are most apparent, any part of the gastrointestinal tract may be involved so patients may also develop diarrhoea.

Which drugs are responsible?

Almost all chemotherapy drugs have a potential to cause mucositis but agents that affect DNA synthesis and are S-phase specific (this is the synthesis phase of the cell cycle) cause the most mucositis.

Examples include:

- Methotrexate
- Anthracycline drugs
- Cylophosphamide.

Management

Mucositis may rarely be life-threatening and when severe, may require the use of feeding tubes. The pain and discomfort from mucositis can greatly impact on the nutritional status of the patient.

Treatment of mucositis is supportive and aimed at symptom control.

- Routine oral care:
    - Removal of dentures
    - Soft cleansing of the mouth and teeth
    - Oral rises with salt and baking soda

    - Regular antiseptic and antifungal mouth washes
- Mucosal coating agents:
    - Topical kaolin/pectin
    - Diphenhydramine
    - Oral antacids
    - Maltodextrin
- Analgesia
    - Ice chips
    - Topical local anaesthetic solutions
    - Topical morphine sulphate in water
    - Oral analgesia or intravenous analgesia with opioids may be needed in more extensive cases

Sclerotic dermal reactions

Scar-like skin reactions that mimic morphoea or systemic sclerosis may accompany the use of bleomycin and docetaxel.

In some cases, these reactions have resolved after the drug has been stopped. The exact mechanism is unknown but it is postulated that these drugs increases the activity of fibroblasts in the skin.

Vascular phenomenon – Raynaud phenomenon and vasculitis

Raynaud phenomenon is an exaggerated response of the blood vessels to cold temperature or emotional stress. The symptoms are that of sharply demarcated color changes of the skin of the digits.

Vasculitis refers to inflammation of the vessel walls and as a result of this inflammation there is compromise to lumen of the vessel causing tissue ischaemia and necrosis.

Vasculitis can present as livedo reticularis, ulceration and thromboembolism (blood clots).

Which drugs are responsible?

Drugs reported to cause Raynaud's phenomenon or vasculitis include:

- Bleomycin
- Cisplatin
- Gemcitabine
- Rituximab.

Management

Correct diagnosis of vasculitis is important and a skin biopsy assists in diagnosis. The treatment of vasculitis involves stopping the offending drug and use of high dose systemic corticosteroids.

Raynaud phenomenon often improves with discontinuation of the drug. Simple measures such as avoiding exposure to cold, hand warmers and the use of protective clothing are universally helpful. Medications that can be used include calcium channel blockers and ACE inhibitors which promote vasodilatations (opening up) of blood vessels in the fingers.

Other including allergic drug reactions and toxic epidermal necrolysis

Like any drug, chemotherapy can cause allergic or non-allergic type drug rashes. Refer to other sections of DermNet for more information about these.

Draft 12 August 2007

Related information

References:

On DermNet NZ:

- Anaphylaxis
- Drug hypersensitivity syndrome
- Fixed drug eruption
- Flagellate erythema
- Drug-induced photosensitivity
- Stevens Johnson syndrome
- Toxic epidermal necrolysis
- Urticaria

Other websites:

Books about skin diseases:

See the DermNet NZ bookstore

Author: Eugene Tan, Medical Registrar, Waikato District Health Board.

DermNet does not provide an on-line consultation service.
If you have any concerns with your skin or its treatment, see a dermatologist for advice.