ARTICLE

The Impact of anti-cancer treatment on feet

Podiatric Adverse Events: Part 2b Dermatological Effects

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Introduction

An increasing population now have 'treatable but not curable cancers'. Whilst part 2a of this article focused on the neurological side effects of 'anti-cancer' treatments, this article discusses the four common dermatological events that can negatively impact the feet and legs as symptomatic podiatric adverse events (PAEs) are common in patients treated for cancer[1]. Radiotherapy, chemotherapy and targeted therapy are all known to cause these dermatological effects, many of which require podiatric treatment.

These dermatological PAEs have a negative effect on patients' physical, functional, emotional, and social well-being[2]. They can be debilitating for someone already struggling with their anticancer treatment regime and a CancerCare survey identified that 'nearly 80% [of patients] were concerned about the actual skin effects they experienced as a result of their treatment and how those side effects – namely irritation, rash and dryness- affected their quality of life' [3].

Publicising these issues (as set out in my previous article), recognising them in a clinical setting, and providing appropriate advice and treatment can be an invaluable part of supporting patients through this difficult time.

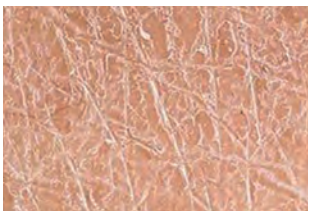
Four Dermatological Podiatric Adverse Events (PAEs)

The four main dermatological PAEs where podiatric-medical intervention is paramount 4 to avert the rapid development of complications associated with anticancer therapy are:

1. **Xerosis**
2. **Hand-foot syndrome (HFS)**
3. **Hand-foot Skin Reactions (HFSR)**
4. **Nail toxicity, dystrophy, inflammation & infections**

Whilst the first three conditions are skin related, they can all occur in conjunction with nail toxicity and dystrophy issues.

It is important to adapt treatment for cancer patients, both to reflect the specific nature of anticancer therapy and anticipate potential complications. By working in partnership with the patient and their cancer team, many problems can be minimised or avoided.



Xerosis

Xerosis (abnormally dry skin) can occur in patients who are receiving either targeted therapy, radiotherapy or chemotherapy[5,6,7].

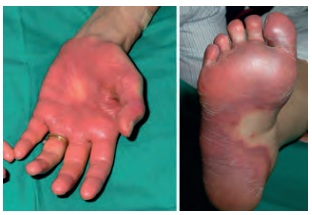
Why does it occur?

The skin is unable to desquamate (shed) and retain hydration due to the impact of anticancer therapies on epidermal keratinocytes.

Many anticancer therapies, particularly those that treat various solid and haematologic tumours, target all rapid proliferation cells including epidermal keratinocytes. This leads to increased trans-epidermal water loss as the therapy lowers the rate of cell turnover. Given there are no oil glands in the soles of the feet, this exacerbates the problem further.

How does it present?

Patients will exhibit with generalised dry skin, erythema, itchiness and/or facial flushing. In my clinical experience, fissures on the lateral aspects of the soles and heels can arise and patients comment that their skin feels tight no matter what they put on it.



Hand-Foot Syndrome (HFS)

HFS, also known as Palmar-Planter Erthrodysesthesia (PPE), causes redness, swelling and pain on the soles of the feet and also on the palms. It is one of the most common adverse reactions to cytotoxic agents.

HFS is graded in severity, although there are a number of different classification systems for doing this. Depending on the grade, some protocols recommend reducing the dosages of some drugs.

Why does it occur?

There are two main theories as to why HFS occurs:

1. There is a greater concentration of keratinocytes in the palms and soles, and these are targeted by cytotoxic agents which focus on fast growing cells. The keratinocytes metabolise the drug quickly and produce a toxin, causing the skin reaction[9].
2. There is a greater concentration of eccrine glands in the palms and soles, and the toxic drug is excreted onto the skin[10].

Either way, we know that HFS can result from more highly concentrated dosages or from low treatment doses over a prolonged period[11].

All of the following drugs have been found to cause HFS:

Anthracycline antibiotics	Doxifluridine	Methotrexate
Capecitabine	Doxorubicin	Mitotane
Cyclophosphamide	Cisplatin	Paclitaxel
Floxuridine	Tegafur	Cytarabine
Fluorouracil	Vinorelbine	Daunorubicin
Mercaptopurine	Etoposide	Docetaxel
Hydroxyurea (hydroxycarbamide)		

How does it present?

Initial symptoms include

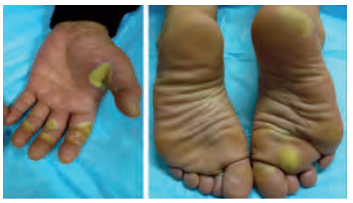
- **Swelling (dysesthesia)**
- **Numbness**
- **Sense of tightness/stiffness**
- **Pain in the palms and/or soles**

Two to four days later, this progresses into a burning pain, accompanied by oedema and bright, well defined, symmetrical erythema on the palms and soles. The patient's palms and soles typically appear to have been stained in red paint and some patients may also see nail changes.

If untreated, skin lesions can progress to painful blistering, desquamated skin cells (flakiness), form crusts and ulceration. With each subsequent cycle of chemotherapy, the reaction will appear more quickly, more severely and can take longer to heal due to the patient's compromised immunity. As the skin is painful to touch, analgesics may be recommended prior to treatment.

DID YOU KNOW?

HFS was first described in 1974 by Zuehlke and was associated with mitotane therapy for hypernephroma (tumour of the kidney)[8].



Hand-Foot Skin Reaction (HFSR)

An HFSR is distinct from, but related to, HFS. On the feet, these painful blisters can limit the patient's mobility and their ability to weight bear properly and lead to an increased chance of a fall. Both HFS and HFSR can be particularly problematic for those patients with active lifestyles or where they are required to stand for long durations.

Why does it occur?

This may be due to increased leakage of the anticancer therapy through mechanical trauma of the skin.

How does it present?

HFSR occurs in areas of friction or pressure in the soles and palms within the first few weeks of anti-cancer treatment. The skin reactions appear as painful blisters, often on pressure points on the feet and develops into hyperkeratotic (callus) areas[12].

All of the following drugs can cause HFSR [13,14,15]***:***

Multikinase inhibitors		
Sorafenib	Sunitinib	Axitinib
Regorafenib	Pazopanib	
Taxanes and Pyrimidine analogues		
5-fluorouracil	Capecitabine	

How can podiatrists help with Xerosis, HFS and HFSR?

Management of these conditions relies on the right intervention at the right time. Physical podiatric treatment is only a small part of this, with support, prevention, and self-care all being key aspects. It is particularly important to take into account the patient's lifestyle and how best to support them in maintaining key elements of their daily activities, as they are already managing significant disruption to their normal routines whilst undergoing anti-cancer treatment.

Education/Preparation

As noted previously, making patients more aware of the podiatric side effects of anti-cancer therapies and the support available, so that they can be prepared for them, can be of great help. Even less severe PAEs can generate disproportionate anxiety and distress in the midst of a cancer treatment programme.

Starting to regularly moisturise the feet prior to starting anti-cancer therapy helps by ensuring the skin is hydrated and combating the excessive desquamation of cells. A urea-based moisturiser can help prevent HFS and HFSR, or extend the time before first occurrence, and reduce symptoms[16,17,18]. Current thinking suggests 10-20% urea-based creams should be used and improvements can be seen within four weeks.

For my patients I typically recommend applying CCS heel balm two or three times daily, particularly after bathing. In my experience, other urea-based creams have been less successful and in some cases patients have complained of stinging, discomfort, pain and peeling. It may be that the CCS urea preparation reacts differently with the secreted anticancer agent and metabolites from the keratinocytes.

Other simple advice can also help – for example on hosiery and nutrition. Using bamboo fibre or rich cotton, seam-free socks helps improve comfort and reduce shearing. Bamboo fibre socks offer additional benefits through moisture and thermo regulation and are anti-bacterial (due to a bacteriostatic bio-agent Bamboo Kun). From a nutritional perspective, some treatments can cause a decrease in Vitamin C, E, B12 and Folic acid[19]. Vitamin B6 (Pyridoxine) has been useful in treating these conditions and alleviating HFS pain[20,21].

For patients at higher risk of HFS or HFSR then educating them about PAEs and highlighting when they should seek urgent assistance can be valuable in getting the right podiatric treatment at the right time.

Podiatric intervention

Providing regular neurological, vascular and biomechanical assessments and good podiatric debridement and nail maintenance is key to preventing further painful complications such as open fissures, ulcerations and paronychia.

For my patients, I aim to schedule their six-weekly appointments two weeks after an IV treatment cycle is administered. This helps reduce the issues in painful weight bearing areas, manage xerosis and detect any neurological changes. In an effort to minimise future issues, I regularly focus on neurology and footwear assessment. Neural disturbance may precipitate falls whilst footwear advice, insoles and exercises can help to avoid irritant trauma in the form of friction, heat, and pressure.

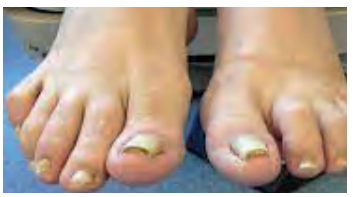
Self-care advice

Foot cooling[22] and a cleansing regime[23,24] are important, particularly for patients suffering from HFS or HFSR. Keeping feet cool helps to reduce swelling and stiffness in the foot and minimises the accumulation or leakage of the drug due to the vasoconstriction effects. Research has cited the use of frozen socks to prevent docetaxel-induced onycholysis and cutaneous toxicity of the foot and shown that wearing a frozen sock for 90 mins during drug administration reduces nail toxicity[25].

I advise patients to wear refrigerated gel socks rather than frozen socks, as the mineral oil impregnated in the socks also improves the moisture content of the skin. Wearing the gel socks for 20 minutes, three times a day has reduced symptoms significantly, with improved healing times and skin integrity.

There are no specific guidelines on skin cleansing but research has shown it to be beneficial[26,27]. It soothes skin irritation and sores, improves desquamation and is important in reducing the risks of infection. For my patients, I recommend regularly bathing the feet in a solution of lukewarm water containing a mixture of Epsom salt and normal table salt. This helps reduce inflammation whilst the magnesium content aids healing of the skin.

For Xerosis, patients should use ointments containing keratolytics (such as salicylic acid 6% with a urea base of 10%-40%) and cover the foot after administration. The need to avoid skin breakdown must be borne in mind in patients with thin and sensitive skin such as diabetic patients. I use Clearzal callus remover, which has delivered good results with close monitoring.



Nail toxicity, dystrophy, inflammation and infections

A large number of anticancer drugs impact the nails, although nails are typically only significantly affected after two months of the patient following a cancer treatment due to the slow growth rate of the nail plate (the drugs affect the kinetics of nail formation).

These PAEs can be extremely painful, severely impacting the quality of life of the patient. The fact that it is another visible sign of the anticancer treatment can also contribute to depression.

Symptoms can last many years after treatment and whilst they are usually reversible after discontinuation of the anti-cancer treatment, in my experience most patients still require ongoing podiatric care.

Why does it occur?

Anticancer drugs distort nail cell growth or the nail toxicity affects the nail fold and nail bed.

All of the following drugs can affect the nails[28]:

Arsenic	Busulfan	Cetuximab
Cyclophosphamide	Bleomycin	Capecitabine
Cisplatin	Dacarbazine	Dactinomycin
Daunorubicin	Docetaxel	Doxorubicin
Etoposide	Fluorouracil	Gefitinib
Hydroxyurea	Idarubicin	Imatinib
Ixabepilone	Melphalan	Mercaptopurine
Methotrexate	Mitomycin	Mitoxantrone
Paclitaxel	Pemetrexed	Sorafenib
Sunitinib	Tegafur	Topotecan
Vincristine		

Nail toxicity can be a particular problem for those receiving epidermal growth factor receptor inhibitors and taxanes.

How does it present?

Cases can involve several, or in some cases all 20, nails.

The nail dystrophies include:

Onychocryptosis	Onycholysis	Onychomadesis
Beau's lines	Mee's lines	Nail growth disruption
Melanonychia	Leukonychia	Paronychia
Splinter haemorrhages and Subungual haematoma		Hypergranulation/ periungual pyogenic granulomas
Taxane-associated acral erythema		Onychauxis/ Onygryphosis
Subungual ulcerations		Fragile nail plate

As a result, patients may have increased difficulty in trimming nails and finding comfortable footwear.

How can podiatrists help?

In general, for those suffering from nail toxicity, timely and preventative podiatric actions can avoid disruption to the patient's treatment cycle and maintain their mobility.

For all nail conditions, it is important to check footwear and hosiery for their impact on pressure areas. Also, the patient may have limited dexterity and mobility due to operations they have undergone during their treatment. As with HFS and HFSR, frozen sock therapy or use of gel socks has been found to significantly reduce nail toxicity, particularly in patients taking docetaxel[29,30].

Providing good routine podiatric debridement and regular, effective sulcal management will help prevent further painful complications such as onycholysis progressing to paronychia, ulcerations and secondary infections. Sulcal management of onycholysis should include removing onychophosis as well as smoothing the sulcal nail area.

For a number of cancer patients, particularly for those with paronychia, nail surgery may not be suitable due to comprised healing times and drug management issues. More frequent sulcal management is key. Nail packs with 1% povidone iodine/ dimethyl sulfoxide[31] or bactigras may be needed to help alleviate pressure, whilst appropriate antibiotics coupled with very salty water footbaths can address unresolved infections (such as Staphylococcus aureus and Pseudomonas aeruginosa (found in more persistent cases))[32].

With onychomycosis it is important to choose the right topical antifungal as some fungal strains will be resistant or not designed to treat that type of fungus. For example, Terbinafine is effective against dermatophytes but less active against candida yeasts and non-dermatophytic moulds, whereas Itraconazole is effective against dermatophytes and candida yeast and some non-dermatophytic mould. In cases of chronic paronychia, the yeast infection Candida albicans has been found.

Conclusion

There are multiple podiatric adverse events (PAEs) that commonly affect cancer patients although this remains relatively poorly publicised. Xerosis, HFS, HFSR and nail-related issues are all known dermatological side-effects of various anti-cancer treatments that can be managed or treated with suitable podiatric advice. There are also neurological PAEs such as peripheral neuropathy and autonomic neuropathy, as covered in part 2a of this article.

Greater awareness of PAEs could significantly help in limiting the negative impact – both through patients being mentally prepared for such issues and being aware of podiatric help being available.

By working more closely with the patient and their cancer unit, podiatrists can improve patients' quality of life and even reduce the chances of patients not finishing their life-enhancing anticancer therapy.

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Afni Shah-Hamilton runs **Tiptoe Foot Care,** a private pain management and podiatry practice in Barnet, London. Afni graduated from University College London in Podiatry BSc (Hons) and completed her master's degree at Kings College London. She currently sits on the Macmillan AHP advisory board and has previously been a member of the national patient safety campaign, Sign up to Safety, advisory group. Afni has worked for Southwark Foot Health Department in conjunction with Guy's and King's College Hospital as well as working for the Society of Chiropodists and Podiatrists (now the Royal College of Podiatry) as a Union Learn Fund Project Worker, promoting learning and development across the profession.

Afni has significant experience of dealing with high risk patients through her close relationships with oncologists and a local cancer charity. She is passionate about the role that podiatrists can play in improving the quality of life for both cancer sufferers and cancer survivors.

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