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**The Impact Impact of anti-cancer treatment on feet**

**Part 3. Podiatric Adverse Events**

**Afni Shah-Hamilton**

Afni considers more problems associated with medication affecting feet when the management of cancer is encountered. These problems have been referred to as Podiatric Adverse Events or PAE’s. In her last article (Part 2) she covered peripheral neuropathy. Hand-foot syndrome, Xerosis, nail toxicity and nail dystrophy will feature in part 3.

# **Hand-Foot Syndrome (HFS**

HFS

is a skin condition also known as *Palmar-Planter Erthrodysesthesia*. It is one of the most common adverse reactions to cytotoxic agents Lacouture (2008). The incidence of HFS varies between 15-45% depending on the agent used in anticancer therapy. The condition occurs because cytotoxic agents target fast growing cells, such as keratinocytes on the palms and soles. This leads to an accumulation of the drug in these areas and it has been suggested that a toxin is created when the drugs metabolise quickly due to an enzyme called thymidine phoshorlase, Asgari (1999) or when they react with sweat, Mroxek-Orlowski (1999).

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| **Drugs causing HFS** |
| Anthracycline antibiotics |
| Cytarabine |
| docetaxel |
| capecitabine (or 5-fluorouacil) |
| doxorubicin |

Initial symptoms are:

* Swelling.
* numbness.
* sense of tightness/stiffness (potentially due to the swelling), and
* pain in the palms and/or soles.

This is followed 2-4 days later by bright well defined, symmetrical erythema on the palms and soles which is accompanied by oedema. Some patients may see nail changes such as onycholysis (see section on nail toxicity). The patient’s palms and soles appear to have been stained in red paint. The redness is less vibrantly shown on Afro-Caribbean and Asian skin but it is still noticeable. If appropriate interventions do not follow skin lesions can progress [Von Moos (2008), Lacouture (2008)] along the lines of;

* painful blistering,
* desquamated skin cells,
* form crusts,
* ulceration.

Prescriptions of Capecitabine cause both skin and nails to be be affected where the skin heals without scarring, unless ulcerations or necrosis has occurred and nails develop paronychia. 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.

Patients with Asian Indian origins tend to be affected by blistering and ulcerations on the heels and lateral borders of the soles, and their skin becomes thin and shiny with deep open fissures.

# **Hand-Foot Skin Reactions (HFSR)**

A related condition that leads to a number of PAEs is HFSR and multikinases inhibitors have been documented to cause HFSR in a significant proportion of patients treated with the agent. Figures have ranged from 20-60%, McLennan (2011), Lacouture (2008), Anderson (2009), Fischer (2013)

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| **Drugs causing HFSR** |
| Multikinase inhibitors - sorafenib and sunitinib, Axitinib |
| Regorafenib |
| Pazopanib |

HFSR occurs in areas of friction or pressure in the soles and palms within the first few weeks of anticancer treatment. This may be due to increased leakage of the anticancer therapy through mechanical trauma of the skin.

The skin reactions appear as painful blisters and develops hyperkeratotic (callus) areas. As these are often located on pressure points on the feet, and can limit the patient’s mobility and their ability to weight bear properly. Due to pain when wearing footwear there is an increased chance of a fall.

## How can podiatrists help with HFS and HFSR?

Management of these two conditions is challenging and relies on the right intervention at the right time. It is also important to take into account the patient’s lifestyle and how best to support them in maintaining key elements of their daily activities, recognising that they are already having to manage a large amount of disruption to their normal routines whilst undergoing treatment. HFS and HFSR can be particularly problematic for those patients with actives lifestyles involving standing for long periods of time.

The following three elements; preparation, podiatric intervention and self care, are key aspects in reducing the impact of these conditions on patients’ quality of life during their treatment.

## *Supporting patients*

Whilst you may not always see patients before they start anticancer treatment, if their course of treatment puts them at higher risk of HFS or HFSR then some preparation work can be a useful preventative approach.

Educating them about HFS and HFSR and highlighting when they should seek urgent assistance can be valuable in getting the right podiatric treatment at the right time. Meanwhile, from a physical perspective, getting patients started on a urea based moisturiser prophylactically before the start of chemotherapy is very beneficial in hydrating the feet and combating the excessive desquamation of cells.

Current thinking suggests 10-20% urea based creams should be used and in the case of patients on Sorafenib, it has been found to reduce the HFSR rates and extended the time before the first occurrence of HFSR, Ren, Z (2015), Lacouture, ME (2008). Urea (20%) based cream used daily, the size of 5p piece can be applied after bathing, twice daily if possible. CCS heel balm is also useful as different urea based creams such as Eucherin, Clearzal, Flexitol (different strengths) and Dermatonics have been less successful and anecdotally patients have complained of stinging, discomfort, pain and peeling when using some of those products. It may be that the CCS urea preparation reacts differently with the secreted anticancer agent and metabolites from the keratinocytes.

## Podiatric treatment

Providing routine podiatric debridement on callus areas and nail maintenance will help prevent further painful complications. Where nails are found to become onycholytic, the podiatrist should cut back all the detached parts of the nail and smooth sulci corners.

Patients can scrub sulci gently on a weekly basis in a salt water solution. Cutting back the nail as much as possible not only prevents further detachment and reduces pressure building up under the nail, it also prevents debris getting underneath the nails which can harbour infection and create discomfort in the shoes.

Two areas to focus on are neurology and footwear assessment. Neurology because neural disturbance may precipitate falls. Footwear advice, insoles and exercises becomes to avoid irritant trauma in the form of friction, heat, pressure, as well as adhesives involved with footwear manufacture. Prevention is important, Scotte, F (2008).

### **Self care advice**

Two elements of self-care advice are important for patients suffering from HFS or HFSR.

Keeping feet cool has been found to help reduce swelling and stiffness occurring in the foot and minimise the chances of any agent leaking through the vessels as the foot stays cooler for longer and reduces the amount expelled out through the eccrine sweat glands. Scotte et al documented in their literature the use of frozen socks to prevent docetaxel-induced onycholysis and cutaneous toxicity of the foot. Meanwhile, Lacouture et al documented variable success of cooling hands and feet in preventing reactions of HFS in those patients receiving paclitaxel, docetaxel and doxorubicin.

Advising patients to wear refrigerated silipos gel socks for 20 minutes, three times a day, has reduced symptoms significantly, particularly during and after chemotherapy administration. Patients have exhibited improved healing times and skin integrity. The mineral oil impregnated in the socks also improves the moisture content of the skin, preventing Xerosis and blistering, potentially making this a more effective solution than frozen socks.

The second key self-care step I recommend is that it is helpful to soothe skin irritation and sores by bathing the feet in a solution of luke warm, very salty water with a handful of Epsom salt and normal table salt for five minutes every couple of days (daily if there are any open sores). Maintaining good hygiene is important in reducing the risks of infection, and the magnesium in the Epsom salts helps reduce inflammation and aids healing of the skin. Sodium chloride salt helps cleanse the skin gently and help reduce infection from the onycholytic nails.

# **Xerosis**

A third PAE includes abnormally dry skin or Xerosis. Fissures on the lateral aspects of the soles and heels can arise because anticancer therapies target all rapid proliferation cells Lacouture, M (2008). This includes epidermal keratinocytes, leading to increased trans epidermal water loss, due to a lower rate of cell turnover and altered cell differentiation.

## How can podiatrists help with Xerosis?

Routine podiatry will help to reduce fissures through scalpel debridement and frequent use of ointments to hydrate the skin. Ointments containing keratolytics such as salicylic acid 6% with a urea base of 10%-40%, and applying an occlusion over the foot after administration e.g. a sock or plastic dressing can be applied. Avoidance of the risk of skin breakdown must be borne in mind in patients with thin and sensitive skin such as diabetic patients. A cream containing a weak trichloraectic acid solution (keratolytic) and urea, such as Clearzal callus remover and available over the counter, can be used. This has delivered good results with close monitoring.

# **Nail toxicity, inflammation and infections**

Lacouture, M et al (2008) considered that approximately 35% of patients suffered nail dystrophy when undergoing anticancer therapies, particularly those receiving epidermal growth factor receptor inhibitors and taxanes.

The nail toxicity affects the nail fold and nail bed. Where anticancer drugs distort the nail cell growth, this can cause:

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| onycholysis,  onychocryptosis,  hypergranulation,  paronychia,  onychauxis,  Taxane-associated acral erythema, and  subungual ulcerations with potential secondary infections. |

Nails are typically affected after two months following cancer treatment. They can be extremely painful, severely impacting the quality of life of the patient and in some cases leading to depression.

One patient stopped her anticancer therapy completely as she found the pain and trauma and appearance of her nails too unbearable.

## How can podiatrists help with nail toxicity?

In general, for those suffering from nail toxicity, timely and preventative actions can avoid disruption to the patient’s treatment cycle and ensure their mobility need not be affected. Management from onycholysis escalating at least tries to stopping further damage to nails affected. Without intervention paronychia and secondary infection of the nail fold and bed can arise even leading to ulceration.

Patients typically cannot undergo nail surgery because of the reduced healing potential. Cotton wool or bactigras nail packs may be needed to help alleviate pressure and prevent the nail curling round. Most nail conditions resolve after the end of the treatment, Goto, H (2016).

As with HFS and HFSR, frozen sock therapy or use of gel socks has been found to reduce nail toxicity, particularly in patients taking docetaxel.

Sulcal management associated with involution and pinch the skin is challenging as the nails start to recover. Unresolved infection with Staphylococcus aureus responds to appropriate antibiotics coupled with very salty water footbaths. Ps. Aeruginosa is often identified in wound cultures. Lomax et al (2016) recommended that first line treatment for acute paronychia should be a combination of amoxicillin with clavulanic acid and in severe cases coupled with surgical intervention.

In the cases of chronic paronychia, the yeast infection Candida albicans has been found. With onychomycosis to is important to choose the right topical antifungal as some fungal strains will be resistant. For example, Terbinafine is effective against dermatophytes but less active against candida yeasts and non-dermatophytic moulds, while Itracoazoles are effective against dermatophytes and candida yeast and some non-dermatophytic moulds. Ciclopirox 8%, Amorolfine and Efinaconazoles have also been recommended as a further alternative. Capriotti et al (2015) found that the use of 1% povidone-iodine / dimethylsulfoxide improved the signs and symptoms of severe paronychia associated with chemotherapy.

**Nail dystrophy**

In this final PAE one of the other side effects of anticancer drugs onychauxis. When co-associated with onychauxis, onychomycosis exploits the patient’s weakened immune system. Thickened and fungal nails may cause distress as a visible sign of their ordeal. Pressure upon the nail bed can lead to pain from subungual ulcerations and increasing the difficulty finding comfortable shoes to walk in. In turn this affects mobility and may cause a delay in the chemotherapy treatment whilst the infections are being dealt with.

Even in cases where the thickening might be considered cosmetic, and as a result be ineligible for treatment under the NHS, it can still be a source of depression and impact on quality of life. However, with regular maintenance and managing infection ulcerations can be prevented. Symptoms can last many years after the patient has had chemotherapy and requires ongoing maintenance.

‘changes are usually asymptomatic and do not require medical intervention... and [are] usually reversible after discontinuation of the anticancer treatment.’ Mischa, PM (2015)

## Conclusion

There are multiple podiatric adverse events (PAEs) that commonly affect cancer patients. The importance of podiatrists working closely with the patient and their cancer unit is productive and beneficial. The inclusion of podiatry is still relatively poorly publicised and understood and so greater awareness is clearly needed.

**Personal reflection**

Taking the time to explain likely issues to my patients and address their concerns has helped them be more positive and resilient during their treatment as they are better prepared mentally for the challenges ahead. Nevertheless, far more could be done to reach the wider population.

Routine podiatric care is strongly recommended from the initial diagnosis of cancer possible but it is essential during the anticancer treatment cycle to manage medication induced nail dystrophy, corns, callus and fissures, blisters, neuropathy and ulcerations.

Symptoms created by changes in gait, increasing the risk of falls occurring, friction from footwear and general foot pain, development of infections and above all dealing with the effect of chemotherapy induced neurological changes warrants support.

PAEs can result in patients suffering severe depression and is *‘often the reason for a patient’s discontinuation of anticancer therapy, with a negative impact on quality of life’* Lacouture M (2008).

Managing many of these side effects not only reduces pain and improves their quality of life but also reduces the chances of them not finishing their life-enhancing anticancer therapy.

**NB: Refer to Parts 1 & 2 for references**

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