Podiatric Adverse Events and Foot Care in Cancer Patients and Survivors

Awareness, Education, and Literature Review

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Cancer is one of the leading causes of mortality and morbidity worldwide. Recent improved therapies have resulted in more patients surviving cancer and living longer. Despite these advances, the majority of patients will develop adverse events from anticancer therapies. Foot alterations, including nail toxicities, hand-foot syndrome, edema, xerosis, hyperkeratosis, and neuropathy, are frequent among cancer patients. These untoward conditions may negatively impact quality of life, and in some cases may result in the interruption or discontinuation of cancer treatments. Appropriate prevention, diagnosis, and management of podiatric adverse events are essential to maintain foot function and health-related quality of life, both of which are critical for the care of cancer patients and survivors. This article shows results related to complaint and impact on quality of life of the Oncology Foot Care program and reviews publications specific to podiatric adverse events related to cancer treatments. (J Am Podiatr Med Assoc 108(6): 508-516, 2018)

Currently, cancer is one of the leading causes of morbidity and death in many high-income countries. Worldwide, an estimated 18.1 million people were diagnosed with cancer in 2018, many of whom died from this disease.[1] Despite these daunting statistics, improvements in cancer therapies have resulted in a greater number of people surviving cancer, with an estimated 43.8 million cancer survivors in 2018. Anticancer therapies may result in adverse events (AEs) that may negatively impact the normal functioning of the feet and lower extremities. Symptomatic podiatric adverse events (pAEs) are common in patients treated for cancer and have considerable negative impact on their well-being and quality of life (QoL). Several questionnaires are available to assess this impact, such as the 14-item hand-foot syndrome–specific QoL questionnaire.[2] These events may have a negative effect on the patient's ability to use footwear, bear weight, ambulate, or perform instrumental or self-care activities of daily life and also may cause treatment discontinuation or modification.[3-6] Because of the potential serious impact and rapid development of complications, podiatric and other medical staff must learn about the prevention and management of the multiple pAEs observed in oncology patients.

This article shows the impact of pAEs on QoL in the Oncology Foot Care program,[7] a program developed to raise awareness among podiatrists training in the Netherlands. Furthermore, this article reviews publications specific to pAEs related to cancer treatments and include peripheral neu-

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ropathy, hand-foot syndrome, hand-foot-skin reaction, nail toxicity, xerosis, edema, and lymphedema.

Awareness and Education

To date, no podiatric screening and treatment strategies have been developed to prevent or mitigate pAEs in cancer patients. Additionally, podiatrists and podologists may not be aware of complications that their treatments can cause during anticancer therapies. The understanding of pAEs related to anticancer therapies by the patient, podiatrist, and oncology team is essential to optimally communicate, manage, and treat these patients.

In 2012, the Netherlands Medical Foot Academy developed an educational program for podiatrists and podologists (ie, Oncology Foot Care program).[7] The main goals of the program are to encourage awareness and screening of potential complications caused by anticancer therapy, to keep the feet of cancer patients in optimal condition during and after therapy, and to encourage communication with the oncology team. A special information booklet is given to cancer patients to make them aware and seek professional help if any pAE arises. Podiatrists could provide valuable information about the condition of the feet to cancer patients, which ensures consistent anticancer therapy for a better QoL.

The Oncology Foot Care program[7] includes psychological topics such as QoL (ie, psychological, social, and emotional characteristics) and risk factors of distress in cancer patients (ie, age, life events). Furthermore, patients report the impact of pAEs on QoL (ie, general activity, mood, walking ability, and life enjoyment) using an 11-point numeric rating scale before and after treatment, where 0 = "no complaint, positive outcome" and 10 = "worst imaginable, negative outcome."

From April to July 2016, the Oncology Foot Care program[7] included a total of 291 patients. The mean age of the patients was 65.3 ± 11.7 years, and the majority of patients (66.3%) were women. The oncology team referred 10.7% of patients, and 18.9% were referred by other health care professionals. The most common cancer was breast cancer (40.2%), followed by colon cancer (10.3%). Before the diagnosis of cancer, 61.5% did not report foot problems. In 67.7% of patients, pAEs were attributed to anticancer therapies. The mean number of visits was 5.9 ± 3.9. Table 1 shows the impact on complaints and QoL of patients that received foot therapy. A total of 106 patients scored their complaint before foot therapy greater than or equal to 8; after podiatric intervention, their level of complaint improved to 4.8 ± 3.0 ($P < .001$). Similar results were scored regarding QoL.

Table 1. Numeric Rating Scale Results Before and After Foot Therapy Regarding Complaints and Impact on Quality of Life

	Before Treatment	After Treatment
Complaint	5.9	3.2[a]
General activity	5.0	3.0[a]
Mood	4.5	2.8[a]
Walking ability	5.1	3.0[a]
Normal work	4.9	3.1[a]
Enjoyment in life	4.4	2.8[a]

[a] $P < .001$.

Most Common Podiatric Adverse Events and Foot Care in Cancer Patients and Survivors

Peripheral Neuropathy

Peripheral neuropathy (PN) is among the most frequent AEs associated with anticancer therapies. Peripheral neuropathy usually begins after several months of anticancer treatment, and could be a persistent complication. The clinical findings include numbness; diminished or absent temperature sensitivity; and alteration of two-point discrimination, touch, vibration, proprioception, and muscle strength, which can lead to imbalance.[8] Chemotherapy-induced peripheral neuropathy (CIPN) is predominantly a sensory neuropathy, known to be a primary dose-limiting toxicity, with a "stocking-glove" distribution, which could extend up to the knees, depending on the amount, frequency, and length of chemotherapy cycles.[9] Chemotherapy-induced peripheral neuropathy develops particularly with the use of platinum, taxanes, alkaloids, thalidomide, lenalidomide, and bortezomib therapies, used to treat solid tumors and hematologic malignancies.[10] Sensory nerves are mainly affected rather than motoneurons, probably because of the lack of protection by the blood-brain barrier and less myelination.[8]

Patients with CIPN may also experience walking difficulties, foot discomfort, and increased propensity to falls.[11] One factor for this is the acute onset of CIPN without adaptation time. Severe neuropathy is also associated with depression[12] and is often a reason for a patient's discontinuation of anticancer therapy, with a negative impact on QoL.[13] The risk of developing neuropathy may be higher in

patients who have other risk factors, such as diabetes mellitus and obesity.[9]

There is no consensus for assessing CIPN and pain, and it is frequently misdiagnosed and undertreated.[14] However, there is a unified terminology criteria for grading any anticancer therapy AE, (Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0) (Table 2). Additionally, multiple specific validated scales (eg, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN 20-item scale,[15] Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity questionnaire,[16] and Neurotoxicity Questionnaire[8]) could be used to measure the impact and severity of neurotoxicity in patients with CIPN. Unfortunately, most of these assessments combine negative and positive symptoms into one question. Because neuropathic pain medication affects only the positive symptoms, the pain-reducing effect cannot be assessed adequately; therefore, we recommend using the Neuropathic Pain Symptom Inventory.[17]

Foot care and a preventive approach for PN is shown in Figure 1. In a previous randomized clinical trial, duloxetine[18] and venlafaxine[19] showed superiority over placebo for controlling pain associated with CIPN. Another relatively positive result was seen in a randomized clinical trial with a combination of baclofen 0.75%, amitriptyline 3%, and ketamine 1.5% gel.[9,20]

Chemotherapy-induced peripheral neuropathy affects proprioceptive feedback negatively, thus disrupting normal locomotion and increasing variability in one's gait.[21] One study showed significantly better balance after 36 weeks of exercise, improved time to regain balance, and improved QoL compared with the control group.[22] Other poorly studied interventions such as sensorimotor training, whole-body vibration, or tai chi may also improve balance.[23] No literature was found regarding the effect of shoes on balance in CIPN. Loss of sensitivity is one of the aspects that leads to inadequate footwear (too large or too small) in the majority of elderly patients, contributing to an increased risk of foot injury caused by shearing forces and skin irritation.[24] Patients with PN preferred lightweight shoes, such as sandals, with a molded foot bed and a tight fit.[25]

Hand-Foot Syndrome

Hand-foot syndrome (HFS) is a common complication of cytotoxic agents (Table 3). Extravasation with accumulation of the drug in the stratum corneum has been hypothesized as a potential mechanism of toxicity.[26] The clinical findings include as first symptoms swelling, numbness, and a feeling of tightness/stiffness or pain in the palms and soles. This is followed 2 to 4 days later by bright erythema and edema, which is symmetrical and well-defined. Onycholysis could be associated with severe reactions. Without appropriate interventions, the lesions can blister, desquamate, form crusts, ulcerate, or even progress to epidermal necrosis (Fig. 2). Healing occurs without scarring unless there has been skin ulceration or necrosis.[26] With each subsequent cycle of chemotherapy, the reaction will appear more quickly, be more severe, and take longer to heal. Common culprits include 5-flourouracil, its prodrug capecitabine, doxorubicin, liposomal doxorubicin, docetaxel, and cytarabine. The incidence of HFS varies depending on the offending agent, ranging from 15% to 45%.[27]

Hand-Foot-Skin Reaction

The multikinase inhibitors, such as sorafenib, sunitinib, axitinib, pazopanib, and regorafenib,

Table 2. General Grading of Common Terminology Criteria for Adverse Events v4.03

Grade	Degree of Severity	General Characteristics
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
3	Severe	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5		Death

Source: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed December 19, 2019. Activities of Daily Living (ADL)

[a]

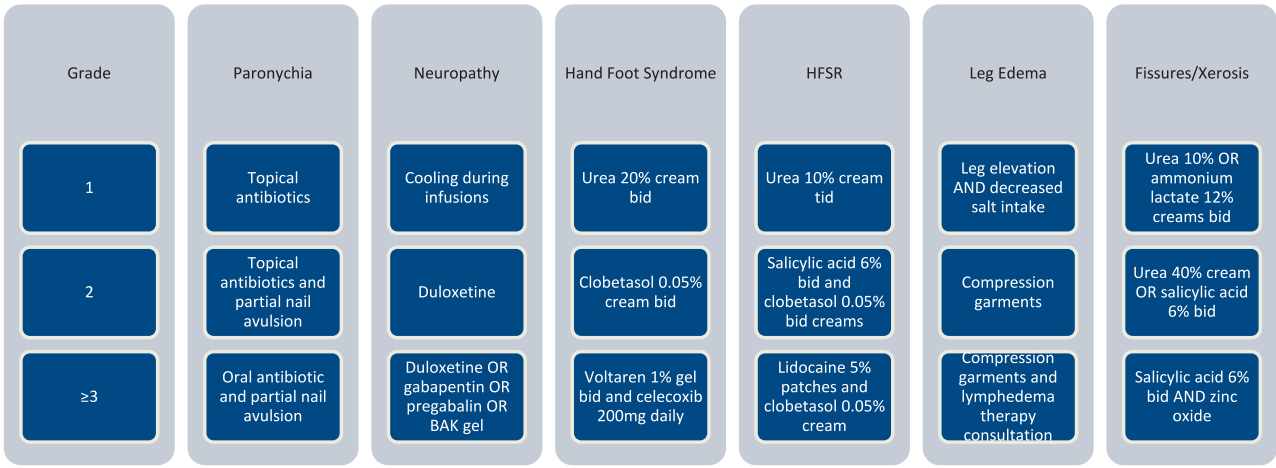

Figure 1. Prevention and management strategies for podiatric adverse events. HFSR, hand-foot-skin reaction; bid, two times per day; BAK, baclofen 0.75%, amitriptyline 3%, and ketamine 1.5%.

may cause hand-foot-skin reaction (HFSR) in 20% to 60% of treated patients. [4,6,28-33] It will occur in areas of friction or pressure in the palms and soles, within the first few weeks, as painful blisters, followed by hyperkeratotic areas, similar to calluses (Fig. 3). This leads to increased pressure points and painful areas on the feet that may limit mobility and weightbearing. Hyperkeratotic HFSR is a painful complication most frequently seen over sites of pressure or friction during the early weeks of multikinase inhibitor therapy.[5] Higher risk is found in Asians, women, and highly active people.

Podiatric Management of HFS and HFSR

Hand-foot syndrome and HFSR could pose a therapeutic challenge, especially when patients are active and when standing for a long time is needed for the patient's daily life. There are few reports in the podiatric literature that discuss preventive therapies for these conditions. Routine podiatric care is highly recommended. Many of the symptoms experienced in the early and late stages of HFS and HFSR are commonly managed by podiatrists (eg, dystrophic toenails/onycholysis, corns and calluses, skin fissures, blisters, neuropathy, and ulcerations). All of the above can be severely painful and debilitating but can be treated conservatively, with minimal discomfort.

Patient education regarding this condition before starting anticancer therapy is important. A preventive approach is based on the use of moisturizer before starting chemotherapy. Avoiding mechanical trauma (ie, caused by footwear) such as that resulting from friction, heat, pressure, irritants, and adhesives may help to limit the reaction.[34] Additionally, cooling of hands and feet during chemotherapy administration have had variable success in preventing the reaction in patients receiving chemotherapies that may cause HFS (eg, paclitaxel, docetaxel, and doxorubicin).[26] Early podiatric evaluation may prevent the progression of HFS and HFSR. Use of good footwear and maintenance of good hygiene play an important role in reducing or minimizing infections that may impact QoL and may limit the use of anticancer

Table 3. Anticancer Therapies and Associated Podiatric Adverse Events

	Cytotoxic Chemotherapy	Targeted Therapy	Radiation Therapy	Surgical Procedures	Stem Cell Transplants
Paronychia	±	+	-	-	±
Neuropathy	+	±	±	-	-
Hand-foot syndrome	+	-	-	-	-
Hand-foot-skin reaction	-	+	-	-	-
Xerosis/fissures	±	+	-	-	±
Edema/lymphedema	+	+	±	±	-
Skin and soft-tissue infections	±	±	+	+	±

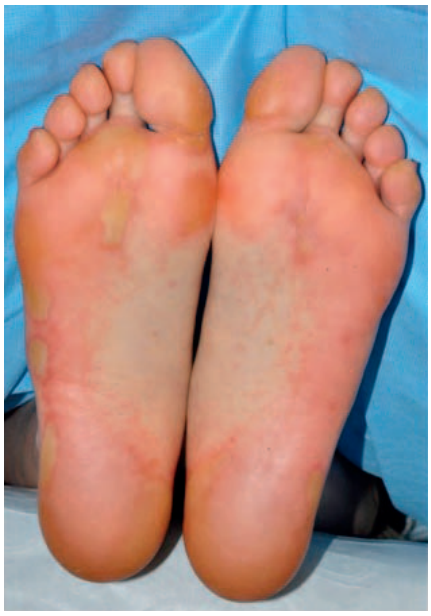

Figure 2. Hand-foot syndrome from cytotoxic chemotherapy (eg, doxorubicin, fluorouracil, and capecitabine).

therapy.[29] A prophylaxis with urea 10% cream in association with supportive care in patients treated with sorafenib reduced HFSR rates, extended the time to first occurrence of HFSR, and improved patient QoL compared with best supportive care.[35] Application of topical nonocclusive polymers in patients with HFSR decreased the specific symptom sum score (eg, scaling, roughness, redness, cracks) and improved QoL compared to baseline.[36]

Nail Toxicity and Infections

Approximately 35% of patients undergoing anticancer therapies may suffer any nail AE.[37,38] Patients receiving epidermal growth factor receptor inhibitors and taxanes are at high risk for developing nail changes, which typically appear after 2 months of treatment.[39] Paronychia, onycholysis, granulation tissue formation, and subungual abscesses with potential secondary infection are often painful and may impact QoL.[38]

Cosmetic nail changes are usually asymptomatic and do not require medical intervention. These nail changes are noted when anticancer therapies affect the nail matrix but usually are reversible after discontinuation of the anticancer treatment.[7] However, nail toxicity that affects the nail fold and nail bed may become symptomatic (Fig. 4). If untreated, it will progress to paronychia or nail detachment and possible secondary infection, requiring dose

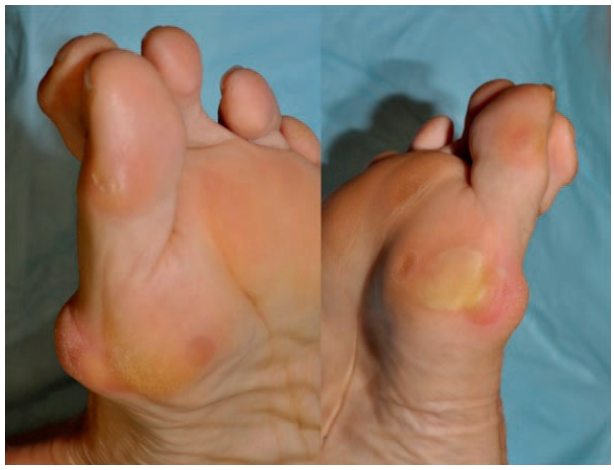

Figure 3. Hand-foot-skin reaction from targeted therapy (ie, multikinase inhibitors such as sorafenib, regorafenib, and sunitinib).

modification or even invasive intervention.[37,38] Prophylactic actions include modifications in shoe wear (proper supportive and contoured shoe). Additionally, cold therapy using frozen socks significantly reduced the incidence of docetaxel-induced foot nail toxicity.[40]

The most common causative infective organism of acute paronychia is *Staphylococcus aureus*. The combination of amoxicillin with clavulanic acid is suggested as first-line treatment for acute bacterial paronychia, together with appropriate surgical drainage if the condition is severe.[41] In cases of chronic paronychia, the most common organism seen is *Candida albicans*.[42] Topical antifungals such as

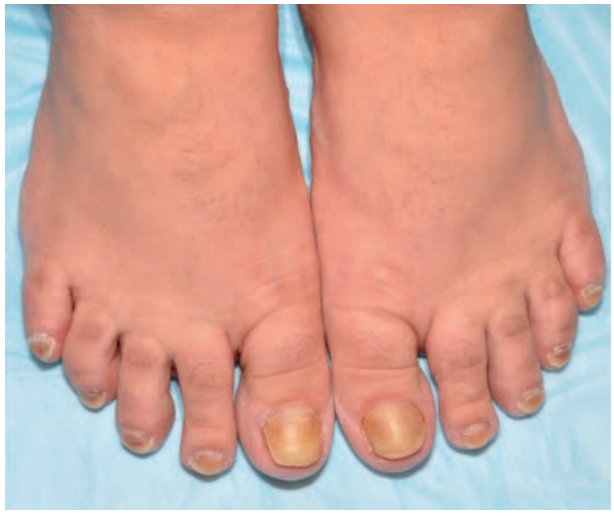

Figure 4. Onycholysis, brittle nails, and paronychia from taxane chemotherapy (ie, paclitaxel and docetaxel).

ciclopirox 8%, amorolfine, and efinaconazole may be used. A case study showed that topical 1% povidone-iodine/dimethylsulfoxide has been very effective in alleviating the signs and symptoms of severe paronychia associated with chemotherapy.[43]

A study of 127 patients with paronychia showed that corticosteroid ointment and phenol chemical matricectomy significantly improved paronychia severity.[44] For recalcitrant cases of chronic paronychia, an alternative therapy with intralesional triamcinolone can be used in the affected nailfold with positive results.[45] If conservative therapy fails, a surgical approach may be necessary. One of the most widely used is a wedge resection of the affected nail fold. Regarding permanent nail procedures, it is important to keep in mind that most of the nail changes in cancer patient will usually resolve after the end of their treatment.

Xerosis

Because anticancer therapies affect all rapidly proliferating cells, epidermal keratinocytes will have a lower rate of turnover, resulting in decreased proliferation and altered differentiation, which increase transepidermal water loss and dryness.[38] It may present as painful fissures in the lateral aspects of the soles and heels (Fig. 5).[46,47] Treatment includes frequent hydration with ointments or creams containing keratolytics (salicylic acid 6%, urea 10%–40%), if possible under occlusion (socks or plastic dressings).[46] For faster healing, liquid bandages (5-hydroqxiquinoline) may be use on fissures.

Edema and Lymphedema

Increased extracellular fluid accumulation in the lower extremities can result from radiation therapy; surgical interventions; or use of chemotherapies in the pelvis, groin, or leg.[48] The result appears to be the same, namely, increased diameter of the leg and foot, with concomitant increased weight, skin changes, infections, and possible ulcerations (Figs. 6 and 7). Treatment and prevention of leg and foot edema is critical for preventing infections and loss of mobility. This is usually achieved through compression garments or manual lymphatic drainage performed by a lymphedema therapist.[48]

Conclusions

Despite the fact that most of the pAEs observed in patients receiving anticancer therapies are not life-threatening, their manifestation may result in dose interruptions or discontinuation and decreased QoL. To date, there has been no podiatric focus on cancer patients and survivors. Moreover, there is a need for clinical trials to develop guidelines for foot care and screening to prevent or reduce complications caused by cancer treatments, similar to the current standardized screening guidelines for patients with conditions such as diabetes and arthritis. A proper education is imperative for providing cancer patients and survivors with the most effective actions against pAEs and to positively impact their QoL. In addition, accurate communication with the oncolo-

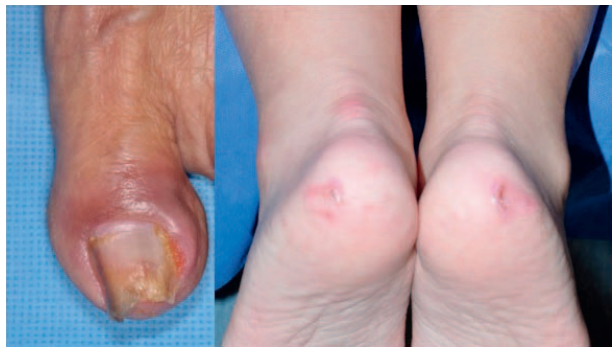

Figure 5. Paronychia and heel fissures with targeted therapies (ie, erlotinib, cetuximab, panitumumab, and afatinib).

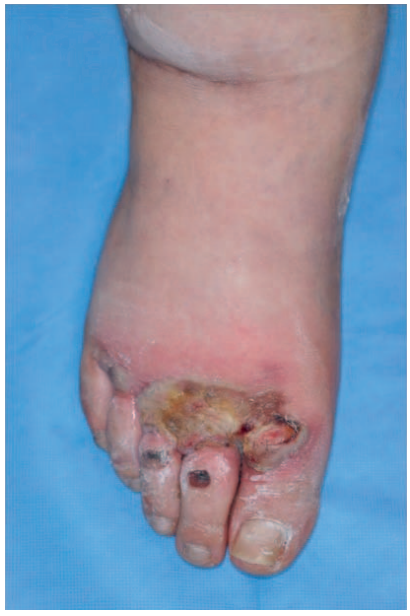

Figure 6. Foot edema from systemic therapies and skin and soft-tissue infection on dorsal foot (ie, chemotherapy and targeted therapy).

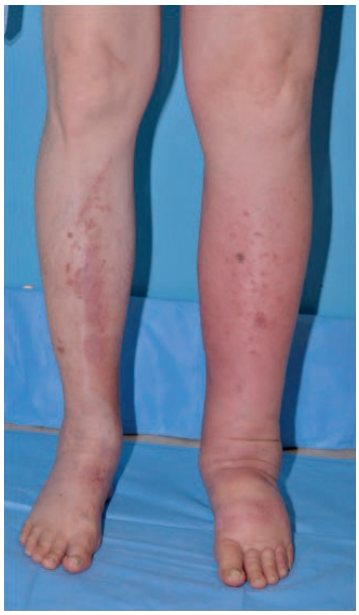

Figure 7. Leg edema caused by chemotherapy.

gy team is needed to properly adjust the cancer treatment and to provide optimal foot treatment at the right moment. The ultimate goal of managing these patients is avoiding treatment modifications or interruptions to attain a maximum benefit from the anticancer agents and the most optimal QoL.

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