ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://nsijournal.com/

Journal of Onychology and Nail Surgery

Letter to Editor

Should refrigerated gloves be replaced by anaesthetic infiltration to avoid nail toxicities from chemotherapeutic agents?

Robert Baran, MD.[1], Bertrand Richert, MD, PhD.[2]

[1]Department of Dermatology, Nail Disease Center, Cannes, France, [2]Department of Dermatology, CHU Brugmann, Brussels, Belgium.

Dear Editor,

Nail toxicities and peripheral neuropathy induced by targeted anti-cancer therapies have been reported extensively.[1] This may, in some instances, necessitate reduction of dosage or even discontinuation of the treatment. It is well known that taxane-related onycholysis is directly correlated to the duration of the infusion, suggesting a direct cytotoxic effect on the nail bed epithelium, with secondary loss of adhesion of the nail plate to the nail bed. An intrinsic antiangiogenic activity of taxanes as well as a phototoxic mechanism have been postulated.[1] Some authors have proposed the secretion of toxic substances through sweat glands as a pathogenetic mechanism, which may explain the hand-foot syndrome but not the associated nail alterations. Another hypothesis proposes the development of toxicities in areas with mechanical pressure (arising of painful callus-like thickening) and repeated trauma where a vascular mechanism is proposed. Even this does not explain the nail alterations as predominant involvement of the dominant fingers/hand is not seen.[2] Thus, the etiopathogenesis of nail alterations with targeted anti-cancer drugs, remains uncertain as none of the hypotheses have been clearly demonstrated.

Scalp hypothermia is provided for limiting hair loss in patients on chemotherapy, based on induction of vasoconstriction, reducing the blood flow as well as drug delivery to hair follicles. Similarly, cooling of the extremities (frozen gloves and socks) has been offered to a large series of patients, to minimise nail alterations. The mechanisms of protection afforded are thought to be due to the near 50% decrease in blood flow to extremities, thus delivering lesser drugs. It also limits the aggregation of microtubules, thereby preventing axonal transport deficit of key cellular components. It also prevents axonal membrane remodelling and, therefore, seems to decrease chemotherapy induced pain, tingling and altered sensations.[3] Though frozen gloves and socks have proven to be safe, their efficacy remains inconsistent, and they are also associated with patient discomfort.[4]

In 2018, we published a series of patients with unilateral sparing from drug-induced nail toxicities and hand-foot syndrome[5], as a consequence of a neurologic condition (central or peripheral nerve palsy). We named it the 'asymmetric acral spared phenomenon'. A drug-induced neurotropic effect is the most plausible explanation for the development of nail alterations with chemotherapeutic agents (mainly taxanes and capecitabine). We, thus, hypothesised that the integrity of central or peripheral nerves is necessary for the development of some acral drug-induced toxicities as taxoids may activate the nociceptive C-fibres that cause neurogenic inflammation, by releasing prostaglandins from the sympathetic postganglionic terminals. Azimi *et al*. have demonstrated that an intact neural component is required for the conventional clinical manifestations of many inflammatory skin diseases: They identified 19 cases of pre-existing inflammatory skin lesions (eczema, psoriasis and bullous pemphigoid) with a near or complete resolution in skin areas where nerves were injured or compromised.[6]

The distal digits have both sensory and autonomic nerve supply.[7] The latter are non-myelinated and end in fine arborisations. Sensory nerves end in either free nerve endings or special end-organ receptors. A dermal network of these unmyelinated free nerve endings is responsible for the perception of pain and temperature. The phenomenon of sparing of extremities with compromised central or peripheral nerve supply, should open up possibilities of newer supportive measures to reduce the neurogenic inflammation induced by some anticancer drugs. These could be more targeted and efficient as compared to the classical approach of causing vasoconstriction with the use of refrigerated gloves and ice packs. In 2001, nail changes of a

***Corresponding author:** Bertrand Richert, Department of Dermatology, CHU Brugmann, Brussels, Belgium. bertrand.richert@chu-brugmann.be

Received: 21 September 2024 **Accepted:** 11 November 2024 **Published:** 29 November 2024 **DOI:** 10.25259/JONS_24_2024

case of 'asymmetric acral spared phenomenon' were reported to improve with an oral cyclooxygenase-2 (COX2) inhibitor.[8] More recently, a study demonstrated that topical diclofenac, a COX2 inhibitor, prevented hand-foot toxicity in patients receiving capecitabine.[9]

Several potential pathways have been identified in capecitabine-induced hand-foot syndrome in a murine model. These include interleukin (IL)-17, arachidonic acid metabolism, p38 mitogen-activated protein kinase (P38 MAPK), nuclear factor-kappa B (NF-κB) and Janus kinase signal transducer and activator of transcription (JAK-STAT3) signalling pathways, which mediate high levels of expression of IL-6 and IL-8, which may also open new supportive ways.[10] Another option could be to block the transmission of the neuronal influx by inhibiting axonal transport in peripheral nerves, to block the neurotropic effect of these drugs. This may be achieved by either of the two proposed options:

1. Ultrasound-guided wrist block: The patient is positioned in a supine position, with the arm laid straight and supinated at mid-forearm level. On scanning proximally, the ulnar nerve is usually seen as an oval hyperechoic structure, immediately medial to the artery. Injection lidocaine (2%) without epinephrine (3–5 Ml) injected after negative aspiration, can cover the nerve circumferentially. This distal peripheral nerve block allows the preservation of proximal muscle function in the upper limb.[11] Only the fingers are numbed, with the block lasting for about 2 h.
2. Intravenous infusion of lidocaine: This technique has been used post-operatively as well as in patients with chronic pain. Intravenous lidocaine has analgesic and anti-inflammatory properties, mediated by an inhibitory effect on ion channels and receptors, thus attenuating the neuroinflammatory response.[12] The therapeutic safety index of lidocaine is high, and the plasma concentrations stay largely below the cardiotoxic and neurotoxic threshold. Side effects include general fatigue, persistent dizziness, or headaches. These are very limited and disappear in 24 hours, making the drug well-tolerated.[13] No numbing of fingers occurs in this modality.

Although, both the procedures use a cheap drug; they require the involvement of an anaesthesiologist, who may not be available at all oncologic centres.

We emphasise the need to look for new ways of limiting nail side effects from chemotherapeutic agents, especially taxanes and capecitabine, which are among the most commonly prescribed anticancer drugs. Nail changes are very common, with some series reporting rates as high as 90% after three treatment cycles.[14] The impact on the quality of life and activities of daily living can be significant and result in treatment interruption. This newer approach of working on the neurotropic mechanisms, is more comfortable for the patient as compared to frozen gloves/socks. Larger clinical trials are needed to establish its efficacy.

Authors' contributions

Dr Baran and Dr Richert participated equally in the designing, the writing and the editing of this paper.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Robert Baran and Dr. Bertrand Richert are on the editorial board of the Journal.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Robert C, Sibaud V, Mateus C, Verschoore M, Charles C, Lanoy E, *et al.* Nail toxicities induced by systemic anticancer treatments. Lancet Oncol 2015;16:e181-9.
2. Ugurel S, Pföhler C, Gutzmer R. Cutaneous adverse events to systemic anticancer therapies: Hand-foot syndrome and nail changes. Dermatologie (Heidelb) 2024;75:451-8.
3. Zajączkowska R, Kocot-Kępska M, Leppert W, Wrzosek A, Mika J, Wordliczek J. Mechanisms of chemotherapy-induced peripheral neuropathy. Int J Mol Sci 2019;20:1451.
4. McCarthy AL, Shaban RZ, Gillespie K, Vick J. Cryotherapy for docetaxel-induced hand and nail toxicity: Randomised control trial. Support Care Cancer 2014;22:1375-83.
5. Baran R, Robert C, Sibaud V. Asymmetric acral spared phenomenon related to systemic anticancer therapies. Skin Appendage Disord 2018;4:315-9.
6. Azimi E, Lerner EA, Elmariah SB. Altered manifestations of skin disease at sites affected by neurological deficit. Br J Dermatol 2015;172:988-93.
7. Morgan A, Baran R, Haneke E. Anatomy of the nail unit in relation of the distal digit. In: Krull E, Zook E, Baran R, Haneke E, editors. Nail surgery a text and Atlas. Philadelphia, PA: Lippincott Williams and Wilkins; 2011. p. 1-28.
8. Wasner G, Hilpert F, Baron R, Pfisterer J. Clinical picture: Nail changes secondary to docetaxel. Lancet 2001;357:910.
9. Santhosh A, Sharma A, Bakhshi S, Kumar A, Sharma V, Malik PS, *et al.* Topical diclofenac for prevention of capecitabine-associated hand-foot syndrome: A double-blind randomized controlled trial. J Clin Oncol 2024;42:1821-9.
10. He X, Wang J, Wang Q, Liu J, Yang X, He L, *et al.* P38 MAPK, NF-

κB, and JAK-STAT3 signaling pathways involved in capecitabine-induced hand-foot syndrome via interleukin 6 or interleukin 8 abnormal expression. Chem Res Toxicol 2022;35:422-30.
11. Sehmbi H, Madjdpour C, Shah UJ, Chin KJ. Ultrasound guided distal peripheral nerve block of the upper limb: A technical review. J Anaesthesiol Clin Pharmacol 2015;31:296-307.
12. van der Wal SE, van den Heuvel SA, Radema SA, van Berkum BF, Vaneker M, Steegers MA, *et al.* The *in vitro* mechanisms and *in vivo* efficacy of intravenous lidocaine on the neuroinflammatory response in acute and chronic pain. Eur J Pain 2016;20:655-74.
13. Beaussier M, Delbos A, Maurice-Szamburski A, Ecoffey C, Mercadal L. Perioperative use of intravenous lidocaine. Drugs 2018;78:1229-46.
14. Winther D, Saunte DM, Knap M, Haahr V, Jensen AB. Nail changes due to docetaxel--a neglected side effect and nuisance for the patient. Support Care Cancer 2007;15:1191-7.

How to cite this article: Baran R, Richert B. Should refrigerated gloves be replaced by anaesthetic infiltration to avoid nail toxicities from chemotherapeutic agents? J Onychol Nail Surg. 2024;1:58-60. doi: 10.25259/JONS_24_2024