

Uncommon Adverse Effects of Commonly Used Chemotherapeutic Agents in Medical Oncology Practice: A Series of Two Cases of Hand-Foot Syndrome

Abstract

Chemotherapy has an increasing potential for cure and palliation of most forms of cancer in different stages. However, its use is associated with a multitude of side effects some very common and few very rare. We present two patients of metastatic nonsmall lung cancer who had severe forms of hand-foot syndrome with two different classes of antineoplastic drugs and have to discontinue chemotherapy.

Keywords: Chemotherapy, cancer, hand-foot syndrome, palliation

Introduction

Chemotherapeutic agents are potentially toxic agents that are associated with a number of side effects including cutaneous ones which include maculopapular rashes, hyperpigmentation, nail changes, Bergdorf's reaction (a form of acral erythema), palmoplantar dysesthesia (palmar-plantar erythematous [PPE]), and hand-foot syndrome (HFS).^[1-4] HFS is a relatively common side effect of many types of chemotherapy drugs, namely, 5-fluorouracil (FU), capecitabine, and liposomal doxorubicin. We present a series of two metastatic nonsmall cell lung cancer patients who developed HFS following vinorelbine- and docetaxel-based single agent chemotherapy which is a rare occurrence.

Case Reports

Case report 1

A 46-year-old male, chronic smoker was diagnosed as adenocarcinoma lung stage IIIB in February 2014. His epidermal growth factor receptor was wild type. He received three cycles of chemotherapy with injection pemetrexed and carboplatin till April. In May, he was reassessed, and there was no change in the size of lung mass. He was given three cycles of injection docetaxel till July 2014. He started with pain back. His bone scan showed increased

tracer uptake in D12-L3 suggestive of bone metastasis. He received 15 Gy/5# local radiotherapy to D12-L3 area and was put on monthly injection zoledronic acid. In view of progressive disease, he was treated with weekly vinorelbine single-agent chemotherapy at 30 mg/m² weekly in October. After 3rd week of single-agent vinorelbine, he started with pain and paresthesias along with reddish discoloration of hands and feet. On examination, symmetrical diffuse erythema and swelling with tenderness were noted in the palms and soles. There was impending desquamation in sole area. Nails were normal [Figure 1a and b]. World Health Organization (WHO) grade 3/4 HFS was diagnosed in him. Chemotherapy was withheld, and patient was treated with local care with emollients and he improved and recovered.

Case report 2

A 52-year-old male, chronic smoker was diagnosed as squamous cell carcinoma lung stage IV at presentation in April 2014. He was started on palliative chemotherapy with gemcitabine and carboplatin. After four cycles in July, he showed signs of progressive disease. He was started on single-agent docetaxel (75 mg/m²)-based chemotherapy. After second cycle of docetaxel in September, he started with pain and paresthesias along with erythema and peeling of skin. On local examination,

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he had symmetrical diffuse erythema with tenderness in the palms and soles. There was diffuse peeling off of skin on palms and soles. Nails were normal [Figure 2a and b]. WHO grade 4 HFS was diagnosed in him. Chemotherapy was withheld, and patient was treated with local care with emollients and he improved and recovered.

Discussion

HFS has been commonly described as a cutaneous side effect of cytotoxic chemotherapy with 5-FU, capecitabine, cytarabine, doxorubicin, liposomal daunorubicin and doxorubicin, gemcitabine and recently with tyrosine-kinase inhibitors such as sunitinib, gefitinib, and erlotinib. Vinorelbine, a promising new chemotherapy agent, has demonstrated activity in different types of tumors including nonsmall cell lung cancer and breast cancer.^[5] As with other vinca alkaloids, vinorelbine acts by inhibiting microtubule assembly, but it seems to have a more acceptable safety profile than those of its predecessors.^[6] This agent is known to cause granulocytopenia, neurotoxicity, asthenia, nausea, alopecia, phlebitis, and constipation, and longer infusion of higher doses of vinorelbine may be associated with HFS.^[5,7,8] Acral erythrodysesthesia was noted in four of sixty patients undergoing single-agent continuous high-dose infusion with vinorelbine for metastatic breast cancer.^[8] It has been postulated that continuous infusion regimens afford the skin longer exposure to the drugs used, thus facilitating drug accumulation. The occurrence of HFS is very rare with vinorelbine use. Docetaxel is a frequently used chemotherapeutic agent belonging to the taxane family. It was first discovered in 1986 and is a semi-synthetic compound derived from the needles of the European yew (*Taxus baccata*).^[9] It exerts its anticancer effect by promoting microtubule stabilization, leading to mitotic arrest and subsequent cell death.^[10] It is used alone or in combination with other chemotherapeutic agents for the management of various malignant conditions including

breast, prostate, gastric, head and neck, and nonsmall cell lung cancer.^[11] Docetaxel is known to cause a number of side effects including hypersensitivity reactions, alopecia, nausea, vomiting, peripheral neuropathy, myelosuppression, diarrhea, mucositis, fluid retention, myalgia, arthralgia, nail changes, and cutaneous reactions.^[11] A number of skin reactions have been described in association with docetaxel, of which limb and/or PPE reactions and fixed plaque erythrodysesthesia are among the more common.^[12] HFS has been reported in association with docetaxel in a number of case reports but remains rare.^[13] The mechanism of HFS is still obscure. However, the high proliferation rate of epidermal basal cells in the palms could make them more sensitive to the local action of cytotoxic drugs. It may also be due to delivery of drugs through eccrine sweat glands, increased vascularization, temperature, and pressure in the hands and feet. Moreover, palms, soles, and finger tips are areas of repeated friction, grasping, and trauma, which further increases the predisposition to this syndrome.^[14] HFS is characterized by paresthesiae in a sock-and-glove distribution, followed by full swelling and erythema. The skin may break down; and in severely affected patients, it desquamates upon discontinuation of therapy. Skin biopsy may show keratinocyte vacuolar degeneration, keratinocyte damage and apoptosis, intracytoplasmic inclusion bodies, dermal perivascular lymphocytic infiltration, and dermal edema.^[15] Management of HFS includes educating the patient regarding the recognition of symptoms and prompt referral. The patient should also be reassured that permanent complications do not occur after the resolution of the events. Extremes of temperature, pressure, and friction should be avoided. Regular application of topical emollients should be advised. Corticosteroids and pyridoxine are found to be effective in the treatment of HFS. In severe cases, further treatment with chemotherapeutic agents is interrupted and can be restarted at a lower dose after resolution of symptoms. Usually, HFS resolves rapidly, often without



Figure 1: (a and b) Palmar and planter erythema, edema, and blisters in right sole after 3 weekly doses of single-agent vinorelbine in a nonsmall cell lung cancer patient



Figure 2: (a and b) Palmar and planter erythema with diffuse skin desquamation after second cycle of single-agent docetaxel in a nonsmall cell lung cancer patient

recurrence. If the symptoms recur with a higher grade, then that particular drug should be discontinued permanently, and alternative drug or treatment plan can be offered to the patient. The possibility of recurrence of symptoms after restarting the chemotherapy could not be observed in our patient as she succumbed to the disease rapidly due to metastasis to lung and liver.

Conclusion

Although HFS is not fatal and is a manageable condition, it is essential to identify this unique syndrome at the earliest to avoid complications and inconvenience in performing day-to-day activities.

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Conflicts of interest

There are no conflicts of interest.

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