Hand–Foot Syndrome following Prolonged Infusion of High Doses of Vinorelbine

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BACKGROUND. The authors reviewed the incidence of toxic skin reactions in patients with metastatic breast carcinoma (MBC) treated with vinorelbine as a continuous infusion.

METHODS. A Phase I/II protocol was designed in which vinorelbine was given as an 8-mg intravenous bolus followed by a 96-hour CI of 7–14 mg/m^2/day. Sixty patients were enrolled in the study: all had MBC and had received prior chemotherapy, and they had no known dermatologic disorder.

RESULTS. Hand-foot syndrome (HFS) developed in 4 of the 60 patients. Patient 1 started with vinorelbine at 12 mg/m^2/day. She developed typical HFS. In the second course, her dose was decreased to 11 mg/m^2/day, but again she experienced HFS. In the third course, dexamethasone was added to the regimen, and no HFS was observed in the remaining six courses. Patient 2 started with a dose of 9 mg/m^2/day. She received four courses without complications; but when the vinorelbine dose was escalated to 10 mg/m^2/day, HFS developed. Patient 3 started with a vinorelbine dose of 14 mg/m^2/day. She developed mucositis during the first two courses and HFS during the third. Patient 4 received vinorelbine at a dose of 13 mg/m^2/day and developed significant HFS. All patients had complete dermatologic recovery. No toxic skin reactions were observed in 14 patients receiving vinorelbine doses of $<$10 mg/m^2/day, whereas 4 of 46 treated at 10–14 mg/m^2/day developed HFS, suggesting a relationship of dose to HFS occurrence.

CONCLUSIONS. Longer infusions of vinorelbine are occasionally associated with HFS. The pathophysiology is not completely clear, but a relationship of HFS occurrence to dose is suggested. Steroids were effective as prophylaxis in one patient. ***Cancer* 1998;82:965–9.** © *1998 American Cancer Society.*

KEYWORDS: hand–foot syndrome, vinorelbine, breast carcinoma, continuous infusion, skin.

Metastatic breast carcinoma (MBC) is the second most common cause of cancer death among women in the United States.[1] In an effort to increase objective response and overall survival rates, a variety of new treatment approaches are currently being studied. They include dose intensification of chemotherapy with hematopoietic stem-cell rescue, changes in the schedule and composition of traditional chemotherapeutic combinations, therapy involving monoclonal antibodies, and novel chemotherapeutic and hormonal agents.[2]

When administered at 30 mg/m^2 weekly, vinorelbine, a new semisynthetic Vinca alkaloid, has produced an objective response rate of approximately 40–50% when used as first-line therapy for MBC and 20–30% when used as salvage therapy.[3] The dose-limiting toxicity of this agent with this schedule is neutropenia. Nonhematologic toxic effects are usually mild and include neurotoxicity (less than with other

Vinca alkaloids), constipation, pain at the injection site, phlebitis, nausea, and asthenia. Less common side effects are alopecia, dyspnea, and paralytic ileus.[3,4] To our knowledge, hand–foot syndrome (HFS) has not been reported to date.

In an effort to improve vinorelbine's efficacy, a Phase I/II protocol was designed at the University of Texas M. D. Anderson Cancer Center, with vinorelbine administered as a 96-hour continuous infusion (CI) repeated every 4 weeks (ongoing trial). We report a new adverse event of that treatment, HFS, which was observed in 4 patients treated on this protocol.

PATIENTS AND METHODS

To date, 60 patients have been enrolled on this study of vinorelbine given as a 96-hour CI. The medical records of 4 patients who developed cutaneous toxic effects suggestive of HFS were reviewed. All patients had received prior chemotherapy, had good performance status (Zubrod < 2), and had no known history of dermatologic disorders.

The treatment plan consisted of an initial intravenous 8 mg/m^2 vinorelbine bolus followed by a 96-hour CI of the same agent (7–14 mg/m^2/day). The chemotherapy was delivered in an outpatient setting with portable infusion pumps.

RESULTS

The clinical presentation of the four patients is summarized in the following case reports.

Case 1

A white woman age 61 years was diagnosed with carcinoma of the left breast in 1968. She developed several recurrences in the left chest wall and received local therapies (surgery and/or radiation). She had metastasis to the lumbar spine, which was treated with spinal irradiation. The patient remained free of disease for 7 years, then a left chest wall lesion again recurred. From 1979 to 1994, the patient received different hormonal drugs and chemotherapy agents; she always achieved some transitory complete remissions, but disease relapsed locally. In January 1996 she received vinorelbine 8 mg as a bolus dose, followed by 12 mg/m^2 as a 24-hour CI repeated for 4 days. The patient developed neutropenic fever and dermatologic changes (Fig. 1). She developed paresthesiae in her palms and soles, which became erythematous and painful. Her skin desquamated in those areas, which remained painful for several days. In the subsequent treatment cycle, the vinorelbine dose was decreased to an 8 mg bolus followed by 11 mg/m^2 continuously for 24 hours $\times$ 4 days. No neutropenic fever was noted, but again the patient developed HFS. Though it was less severe (with the pain having a shorter duration) and better tolerated at this dose level, the HFS had the same general characteristics as in the first course. The patient achieved a partial response (PR), and a decision was made to continue with the same regimen and add dexamethasone, 8 mg orally twice a day for 5 days, starting just prior to each vinorelbine bolus. The patient received four more uneventful vinorelbine courses at the same doses, with the same premedication. No HFS developed. After the seventh course, she was removed from the study because of disease progression.

Case 2

A white woman age 30 years was referred to our institution with a Stage IV infiltrating ductal carcinoma of the right breast and metastasis to the liver. The patient received CMF (cyclophosphamide, methotrexate, and fluorouracil), anthracycline-based chemotherapy, and docetaxel. She was then enrolled on the study of 96-hour CI vinorelbine. Her initial regimen consisted of an 8 mg vinorelbine bolus followed by 9 mg/m^2 CI for 24 hours $\times$ 4 days. She received a total of four courses at this level without any significant side effects. Because her disease remained stable, the daily doses were escalated to 10 mg/m^2, with the bolus dose remaining at 8 mg. She received two courses at this escalated dose; on both occasions, she developed erythema of both feet with blistering of skin following completion of chemotherapy. The patient was seen by a dermatologist, and infectious (including fungal) causes were ruled out. The cancer continued to progress, and the patient was removed from the protocol.

Case 3

A white woman age 51 years was diagnosed with a Stage II infiltrating ductal carcinoma. She received four cycles of anthracycline-based adjuvant chemotherapy. In June 1995 she developed bone and liver metastases, and treatment with docetaxel and cyclophosphamide was begun. After the patient achieved an initial PR, her disease progressed. Vinorelbine was given initially as a bolus of 8 mg followed by a dose of 14 mg/m^2 CI $\times$ 4 days. In the first two courses, the patient experienced significant mucositis and in the third course, significant HFS, which started as erythema in the hands and feet, followed by desquamation after completion of the CI. The HFS resolved spontaneously. As her disease progressed, the patient was removed from the trial.

Case 4

A white woman age 61 years was diagnosed with Stage II carcinoma of the left breast. She received eight cy-

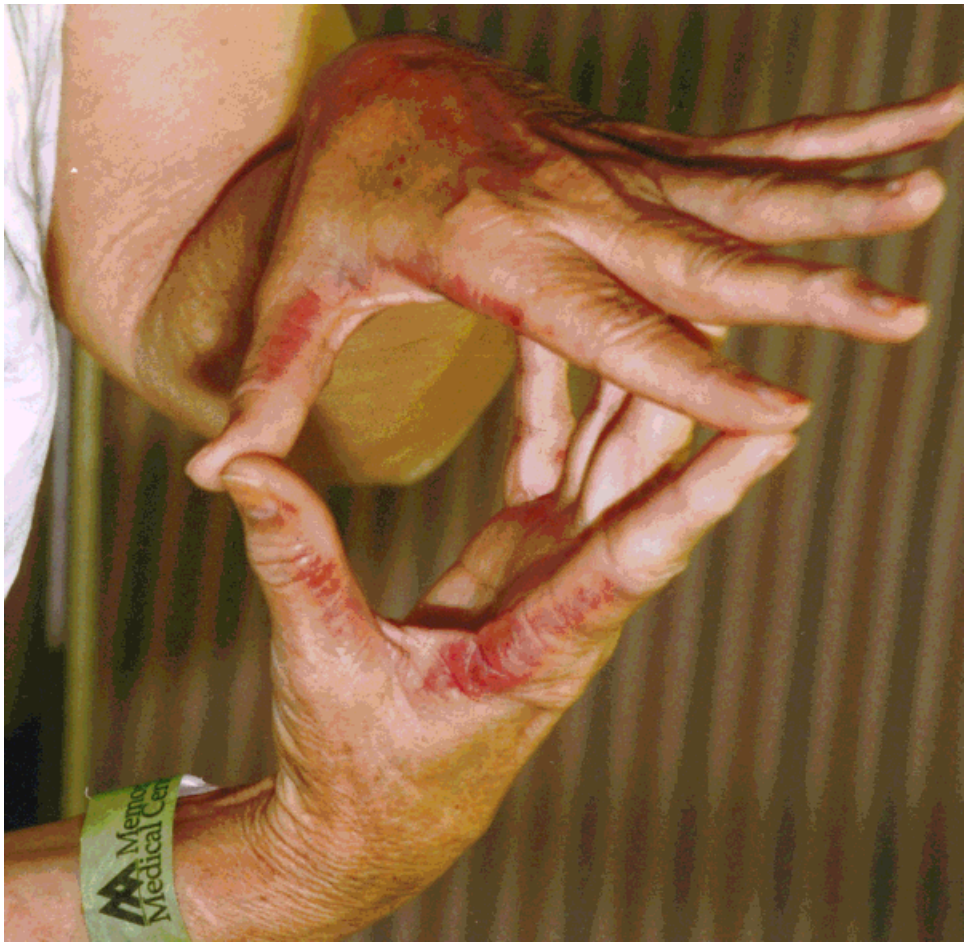

FIGURE 1. A detail of erythema in the hands of Patient 1 is shown.

cles of anthracycline-based adjuvant chemotherapy. In 1992 she presented with recurrent disease in the chest wall and was given six cycles of anthracycline-based chemotherapy followed by radiotherapy. After that, the patient continued to have no evidence of disease until the end of 1994, when her disease again recurred. She was administered paclitaxel but failed to improve. The patient was enrolled in the CI vinorelbine study and received an 8 mg bolus followed by 13 mg/m^2 CI for 24 hours $\times$ 4 days. The patient developed significant mucositis and HFS (Fig. 2); this improved slowly after treatment was completed. This patient's clinical course was similar to those of the patients described above. However, her hands were not affected. The patient relocated and was removed from the study. No follow-up information is available.

DISCUSSION

Vinorelbine, a promising new chemotherapy agent, has demonstrated activity in different types of tumors, including nonsmall cell lung carcinoma and breast carcinoma.[3] 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.[5] This agent is known to cause granulocytopenia, neurotoxicity, asthenia, nausea, alopecia, phlebitis, and constipation.[3,4] Those side effects were observed during treatment with the weekly regimen. We previously reported that in patients with refractory MBC, a CI of vinblastine produced higher antitumor activity than did short infusions of that agent.[6] A recent study with a CI of vinorelbine also demonstrated significant activity in patients with previously treated MBC.[7] We thus initiated a trial of vinorelbine using a different schedule, in an effort to maximize the drug's efficacy.

With the revised dosing schedule, we encountered a different adverse effect, HFS. Also known as palmar–plantar erythrodysesthesia, HFS is a pathologic process first described in 1984 by Lokich and Moore[8] in patients receiving CI of several chemotherapy agents. HFS has been strongly associated with CI of 5-fluorouracil, at an incidence ranging

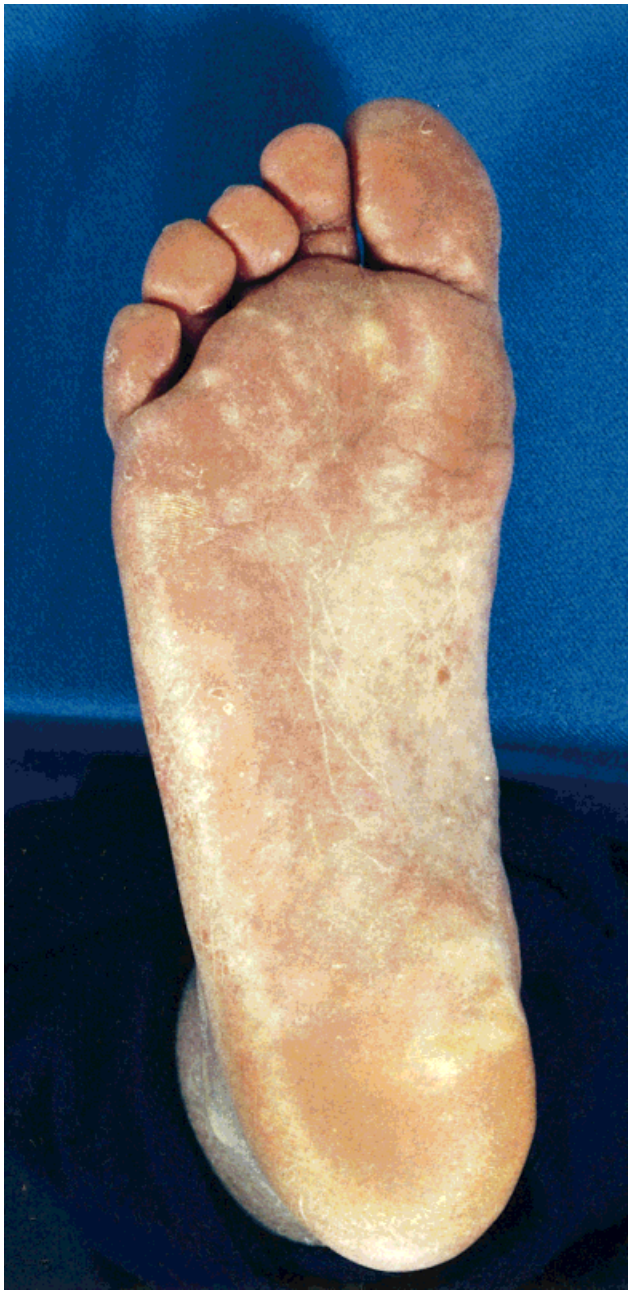

FIGURE 2. Desquamating plantar lesions seen in Patient 4 are shown.

from 7.5% to 25% of patients so treated.[9] It has been postulated that CI regimens afford the skin longer exposure to the drugs used, thus facilitating drug accumulation. HFS is characterized by paresthesiae in a sock-and-glove distribution, followed by painful swelling and erythema. The skin may break down; and in severely affected patients, it desquamates upon discontinuation of therapy. Different histologic patterns have been described in the past.[8–10] More recently, Gordon et al. described two cases of HFS caused by administration of liposomal doxorubicin[10] and suggested the possibility of the drug's having a direct toxic effect on basal keratinocytes. Unfortunately, no biopsy samples were obtained from our patients during the acute phase of the HFS. At the M. D. Anderson Cancer Center, despite extensive use of CIs of doxorubicin and vinblastine, we have not observed HFS in a significant number of patients.

The syndrome improves with discontinuation of therapy, and the skin regenerates normally. Some authors advocate the use of pyridoxine[11] or a vinorelbine dose reduction in affected individuals. In one of our patients, dexamethasone was administered concomitantly with the vinorelbine infusion, and the patient was able to continue receiving chemotherapy in subsequent courses without developing new episodes of HFS. It is also interesting to note that in our Case 2, the HFS only developed after the vinorelbine dose was escalated, suggesting a dose–response correlation. Toussaint et al.[7] did not report any HFS cases when vinorelbine doses were below 10 mg/m^2/day. Of the 60 patients in our study, 14 received vinorelbine doses below 10 mg/m^2/day and did not develop HFS, whereas 4 of 46 patients who received higher doses did develop the skin changes. In HFS-affected patients, an attempt to continue vinorelbine treatment at a reduced dose in subsequent courses seems justifiable.

In summary, longer infusion of higher doses of vinorelbine may be associated with HFS. This had not been reported with vinorelbine given as a bolus. We herein described 4 cases of HFS noted among 60 patients enrolled in our study of a 96-hour CI of vinorelbine. The preliminary overall incidence (7%) of HFS observed so far is similar to that noted in patients treated with a CI of 5-fluorouracil. This side effect may be related to the administration schedule as well as to the doses of the chemotherapeutic agents used. The physiopathology remains unclear. Premedication with steroids appeared effective in blocking the effect, but prospective studies are needed to clarify this matter further and to compare the efficacy of steroids with that of pyridoxine.

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