# Hand-Foot Syndrome Tied to New Cancer Drug

BY MIRIAM E. TUCKER
*Senior Writer*

STOWE, VT. — A "striking" erythematous, peeling eruption of the distal extremities associated with a new cancer drug will be seen increasingly in physicians' offices, Dr. Peter W. Heald predicted at a dermatology conference sponsored by the University of Vermont.

The drug, sorafenib, was approved in 2005 for the treatment of advanced renal cell carcinoma. Codeveloped by Bayer Pharmaceuticals and Onyx Pharmaceuticals Inc. under the name Nexavar, the agent is a multikinase inhibitor of tumor-cell proliferation and angiogenesis. It is currently being evaluated for a variety of other tumors, including melanoma.

In the meantime, some patients with advanced melanoma who are unable to tolerate interferon have been treated with the oral medication. "This is being used off-label for melanoma, even though the melanoma trials are still in progress at this point," said Dr. Heald, professor of dermatology at Yale University, New Haven, Conn.

A recently published phase III randomized, double-blind placebo-controlled trial of oral sorafenib (400 mg twice daily) in 903 patients with advanced clear-cell renal cell carcinoma demonstrated a significant increase in progression-free survival (5.5 months vs. 2.8 months). However, the treatment was associated with a variety of adverse effects, including the hand-foot skin reaction in 30% of the patients (median treatment duration 23 weeks), compared with just 7% (median 12 weeks) in the placebo group (N. Engl. J. Med. 2007;356:125-34).

"If you haven't seen this, I can tell you it's coming to a patient near you as the use of this drug picks up. Now that the drug is on the market, off-label use will increase along with its use in management of renal cell carcinoma," said Dr. Heald, who is also attending dermatologist at the West Haven (Conn.) VA Medical Center.

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DR. HEALD

Most of the literature on sorafenib hand-foot syndrome comes from the oncology community and is "a little murky at the moment," he said.

The eruption presents in a spectrum ranging from peeling to bullae and erosions, and also appears to have a vascular component. In one case report, the authors described what they considered to be "leukocytoclastic vasculitis masquerading as hand-foot syndrome" in a 70-year-old man with metastatic lung cancer who was taking sorafenib (Arch. Dermatol. 2006;142:1510-1).

But Dr. Heald says he believes that the vascular component is part of the spectrum of sorafenib hand-foot syndrome, describing one of his patients with venous insufficiency in whom the skin manifestation of the syndrome was worse in the more severely affected limb.

The syndrome does appear to be dose dependent. In a pooled analysis of four phase I dose-escalation trials of sorafenib, few patients experienced it at dosages less than 300 mg twice daily, but both frequency and severity of the skin eruption increased with dosages of 300-600 mg b.i.d. At the recommended dosage of 400 mg b.i.d., 15% of patients experienced hand-foot syndrome of grade 2 or 3 (Eur. J. Cancer 2006;42:548-56).

As with the drug eruptions that occur with epidermal growth factor inhibitors such as cetuximab and erlotinib, the patients who experienced sorafenib hand-foot syndrome had significantly longer times to progression than did those who did not experience the skin toxicity.

Some oncologists believe that the sorafenib-associated syndrome is the same as the drug eruption known as "Ara-C syndrome," a painful erythematous palmar/plantar eruption seen in leukemia patients receiving intravenous treatment with cytosine arabinoside (Ara-C).

Dr. Heald disagreed, though, noting that Ara-C syndrome doesn't cause the "funky split peeling" that is worse distally and improves farther up the limb, basically disappearing above the elbow or knee.

Treatment of sorafenib hand-foot syndrome depends on its severity. Topical steroids to minimize the peeling usually suffice for patients with grade 1 disease involving minimal erythema. Topical steroids should also be tried first in patients with grade 2 disease, defined as peeling, bullae, and edema that don't interfere with activities of daily living. Keratinolytic agents such as urea may be helpful in these patients as well, he said.

But for patients with grade 2 disease that is refractory to topical steroids and for those with grade 3 disease that interferes with activities of daily living, Dr. Heald recommended working with the patient's oncologist to interrupt the sorafenib therapy and restart it at a lower dose. In the published phase III trial, doses were reduced in 13% and interrupted in 21% of the sorafenib group because of adverse events, most of which were due to hand-foot skin reactions or gastrointestinal events.

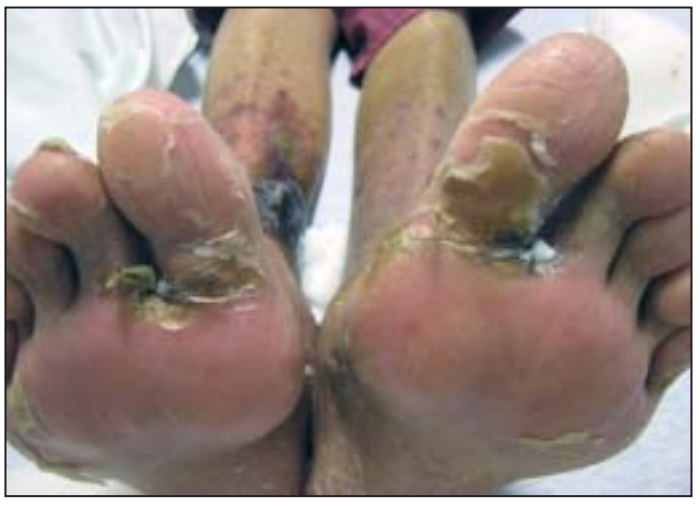
As the off-label use of sorafenib increases for the treatment of a variety of cancers, physicians will be seeing increasing numbers of patients taking the drug. In addition to the hand-foot syndrome, 40% of the patients in the phase III trial experienced rash/desquamation, 27% had alopecia, and 19% had pruritus, compared with 2% or less of those adverse events in the placebo group.

Currently, investigators are looking at additional uses for sorafenib. One published phase II study involving 37 patients with advanced melanoma found little or no antitumor activity with 400 mg b.i.d. sorafenib monotherapy (Brit. J. Cancer 2006;95:581-6), and a manufacturer-funded, phase II randomized trial of sorafenib or placebo in combination with carboplatin and paclitaxel as second-line therapy in 277 patients with advanced melanoma failed to reach its primary end point of progression-free survival.

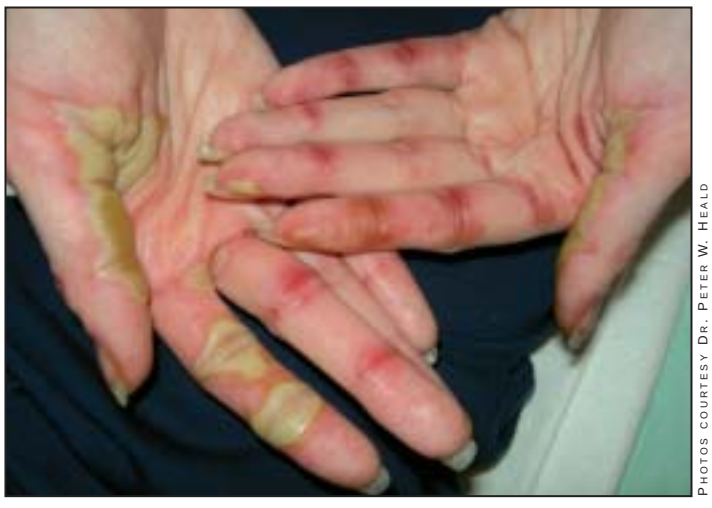
Bayer and Onyx, however, are continuing to investigate the drug's use in melanoma. An ongoing phase II study using sorafenib in combination with dacarbazine as first-line therapy has thus far shown a 50% improvement in progression-free survival, Onyx spokesperson Julie Wood said in an interview.

At the same time, at least two other externally sponsored phase II studies are also looking at combination therapy with sorafenib in treating melanoma. Other trials are investigating its use for liver, lung, and breast cancer, she said.

In any case, Dr. Heald noted, "As use of this drug spreads out from renal cell carcinoma, we'll be seeing more and more hand-foot syndrome." ■



**Grade 2 hand-foot syndrome, causing peeling on the plantar surface, is shown on a man who took sorafenib for 2 months.**



**Grade 3 syndrome appeared as hemorrhagic, pustular acral lesions on the hands of this patient who needed a lower dose.**

PHOTOS COURTESY DR. PETER W. HEALD

# Melasma, Undertreated in Men, Clears With Topical Solution

BY HEIDI SPLETE
*Senior Writer*

GRAND CAYMAN, CAYMAN ISLANDS — A topical solution containing 2% mequinol and 0.01% tretinoin can noticeably improve facial melasma in men, based on results from a small study presented at the Caribbean Dermatology Symposium.

Male melasma is undertreated, in part because many men are ashamed to seek help given the condition's association with women and pregnancy, said Dr. Jon Keeling, a dermatology resident at Wellington Regional Medical Center in West Palm Beach, Fla.

"There are no previous reports of using mequinol in the treatment of melasma in women or men," he said. Dr. Keeling presented the data on behalf of Dr. Marta I. Rendon, who conducted the study at her private dermatology practice in Boca Raton, Fla.

Five healthy men aged 30-45 years with at least a 1-year history of melasma were instructed to apply a 2% mequinol/0.01% tretinoin solution nightly for 12 weeks along with a 6% zinc oxide sunscreen with SPF 30 each day. All of the patients had failed at least one previous treatment for melasma.

After 12 weeks, four of the five patients' faces were cleared, based on physician assessment, patient self-assessment, and evaluations of standardized photos taken at 2, 4, 8, 12, and 16 weeks after baseline.

The fifth patient had partial clearance after 12 weeks, Dr. Keeling said.

All patients showed some improvement after 4 weeks and the maximum improvement after 12 weeks of treatment. Their skin remained clear 16 weeks after the start of the study.

Overall, the medication was well tolerated; one patient reported mild stinging when he applied the solution.

"It is important to note the psychosocial impact of melasma for men," said Dr. Keeling, adding that the number of men seeking treatment for skin pigment problems is rapidly growing. ■