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Mike Blaylock's rash developed quickly after colon cancer treatment with an EGFR inhibitor.

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Why a Rash?

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Finding Hope

A Rash of Good News

Side effect may predict response to treatment.

By Stacie Z. Berg

When standard chemotherapy failed to stop his stage 4 colon cancer from progressing, Mike Blaylock began a combination of Erbitux (cetuximab) and Camptosar (irinotecan). He got "the rash," as he calls it, immediately after beginning the new treatment.

Blaylock, a vice president at the University of Mobile in Alabama, had acne on his face and a chickenpoxlike rash on his back, chest, and legs. "It was like being a teenager again," he says. But while the rash wasn't pretty, it was a good sign the drug was killing the cancer.

Although a rash isn't usually a welcomed sight, patients being treated with drugs that target the epidermal growth factor receptor, or EGFR, often feel relieved, at least initially, when they develop one. Studies show those who develop a rash often have a better response to the drug and live longer. The good news is you don't have to live with the rash, which can be itchy and possibly disfiguring.

Most people think having a rash is something they have to deal with, says Mario E. Lacouture, MD, director of the Cancer Skin Care Program at the Robert H. Lurie Comprehensive Cancer Center in Chicago. But because these rashes can lead to infection and ultimately a delay or stop in treatment, doctors take them very seriously. "Doses are less likely to be reduced or modified if we can [treat rashes early]," Dr. Lacouture says.

Predictive Yet Worrisome

Patients primarily experience acne-like rashes on the face, neck, chest, and back, which vary in severity, but are typically mild to moderate. While timelines vary, most patients develop the rash during the first week of treatment, presenting as a red and inflamed rash (erythema) with swelling, followed by an acne-like rash called papulopustular eruption during the first three weeks.

The rash usually peaks during the first couple of weeks, and dries up within a month. Patients may have dry skin and pruritis, and redness may develop. In addition, hair can thin out and tissue surrounding the nail bed can become inflamed.

Approved EGFR inhibitors known to cause rash include Erbitux, Tarceva (erlotinib), Vectibix (panitumumab), Nexavar (sorafenib), Sutent (sunitinib), and Tykerb (lapatinib). The incidence of rash varies based on the type of cancer and drug used. For instance, skin rash occurs in up to 90 percent of patients treated with Erbitux, while other drugs may only affect half of patients.

Multiple studies demonstrate the correlation of rash between EGFR inhibitors and prolonged survival among patients with non-small cell lung cancer, colorectal, kidney, pancreatic, head and neck, and ovarian cancers.

In patients with metastatic colorectal cancer, a study published in the *New England Journal of Medicine* showed patients who had skin reactions had higher response rates to Erbitux with or without Camptosar. More than 25 percent of patients who developed a rash saw their cancer respond to the combination compared with only 6.3 percent of patients who did not have a rash. Among those who took Erbitux alone, 13 percent of patients who had a rash responded to treatment compared with none in the group without rash.

Trials of Tarceva showed a correlation between rash severity and drug effectiveness. In one study, advanced nonsmall cell lung cancer patients who received Tarceva and developed a grade 2/3 rash survived, on average, 19.6 months compared with patients with no rash, who survived a median of 1.5 months. Other Tarceva studies show similar results with head and neck and ovarian cancer patients. Experts caution, however, that it's important to note that association between rash severity and survival remains to be validated in randomized studies with long-term follow-up.

Although rash may signify the drug is working, it does not mean the rash shouldn't be treated.

Research continues to determine if the drugs work in patients who don't develop a rash. "That's the problem. We don't know that," says Roman Perez-Solar, MD, chairman of medical oncology at the Albert Einstein College of Medicine and Montefiore Medical Center in New York. "There's not enough evidence."

For some patients, rash may be a delayed effect. Nicholas Kraus, a 64-year-old scientist who describes himself as a "lifetime radical non-smoker," was diagnosed in September 2005 with stage 4 lung cancer. Treated with Tarceva, Kraus developed a rash—but only after a couple of months—on his face and neck as an acne- and sunburn-like rash.

Treating Rash

Although rash may signify the drug is working, it does not mean the rash shouldn't be treated. A severe rash can develop into an infection, which can delay treatment or necessitate a dose reduction, which is why it's so important to treat a rash before it becomes severe, doctors say.

"If the rash is not well controlled, you can get infected anywhere there's a hair follicle," says Ed Kim, MD, assistant professor of thoracic/head and neck medical oncology at Houston's M.D. Anderson Cancer Center. When EGFR inhibitors were first introduced and patients developed a rash, "physicians would stop giving the drug because of relative unfamiliarity of treatment of side effects," says Dr. Kim.

While there's still no widespread consensus, new guidelines have been developed based on two recent studies, says Dr. Lacouture. The first was a phase III study presented at the 2007 annual meeting of the American Society of Clinical Oncology showing that the antibiotic tetracycline was effective in managing rash. The second study, presented at the 2007 annual meeting of the American Academy of Dermatology, found minocycline improved rash severity and could possibly be recommended as a preventive measure during the first few weeks of Erbitux treatment.

In May 2007, *The Oncologist* proposed a breakdown of rash severity and treatment guidelines. A mild rash, defined as a localized acne-like rash with no signs of infection and minimal impact on daily activities, can either be watched or treated with an over-the-counter topical hydrocortisone cream or clindamycin, an antibiotic gel. (Doctors recommend not using over-the-counter acne medications or alcohol-based lotions or gels. Emollients, such as Eucerin, Cetaphil, and Aquaphor may be helpful in soothing and healing rash on the hands and feet.)

For a moderate rash, which is a more spread-out rash with mild pruritus or tenderness but no signs of infection and no impact on daily activities, the guidelines recommend treatments include a stronger topical hydrocortisone cream, clindamycin, or Elidel (pimecrolimus), a cream used to treat eczema, plus oral antibiotics doxycycline or minocycline.

Treatment for a severe rash with severe pruritus or tenderness that covers a wide area, impacts daily activities, and is infected or has the potential to become infected, is the same as that for a moderate rash but with the addition of Medrol (methylprednisolone), a topical steroid drug to suppress inflammation. Cancer treatment dose may be reduced until the infection is under control. If improvement is not seen within two to four weeks, an interruption in therapy is recommended.

Within a week of starting treatment for stage 4 lung cancer, 62-year-old Daryl Gilbert's face completely broke out with an acne-like rash. Caused by Tarceva, it subsequently spread to her arms, legs, and buttocks. Dr. Lacouture started Gilbert on an oral antibiotic and creams and called her every three days to see if the rash improved.

After trying several drugs and creams, it was the acne drug Accutane (isotretinoin) that reduced the symptoms. (Accutane is only used when other interventions have failed and the

patient's tumor is responding to the EGFR inhibitor.) Because of Dr. Lacouture's encouragement and suggestions, Gilbert didn't have to stop treatment to deal with the rash symptoms.

Kraus and Blaylock both had minor treatments to manage their rashes. Kraus underwent a cycle of oral antibiotic and Blaylock tried special soaps, which didn't work, but found the antihistamine Benadryl (diphenhydramine) reduced the itching.

Dr. Kim treats his patients prophylactically—a strategy that “has really helped us not have to wait until the patient comes into the doctor's office, [and has helped us not] have to withhold the drug.” While other options for treatment-related rash are being studied, “how can one compete with antibiotics and steroids? They are inexpensive and work pretty effectively,” Dr. Kim says. Even with treatment, the appearance of a rash hits everyone differently. For Gilbert, who runs market research groups, it was “discouraging to have this rash all over my face. You just don't feel very good about yourself,” she says. “It's like wearing cancer on your face. Every time you look in the mirror, it's like reminding yourself you have cancer.”

But it's that correlation that has Blaylock saying, “I don't mind looking bad when the cancer's being killed. It's better than lying in the coffin and having people say, ‘My, doesn't he look good.’”