

Vorinostat in cutaneous T-cell lymphoma

Novel histone deacetylase inhibitor can delay disease progression in patients who are resistant or refractory to other systemic therapies

What's new, what's important

A new set of terms is coming to the bedside: "epigenetics" and "histone deacetylase (HDAC) inhibitors." Epigenetics—literally "on genes"—refers to all modifications to genes other than changes in the DNA sequence itself. An example of an epigenetic mechanism is histone acetylation. Histones are a family of nuclear proteins that interact with DNA, wrapping it around a core of histone octamer within the nucleosome. Emerging as a new class of drugs, HDAC inhibitors may well play a major role in cancer treatment. They can block angiogenesis and cell cycling and promote apoptosis and differentiation.

Vorinostat is an HDAC inhibitor, indicated for cutaneous manifestations of cutaneous T-cell lymphoma. The dose is 400 mg PO daily.

— Jame Abraham, MD
Section Editor

A number of hematologic and solid malignancies feature alterations in histone acetylase regulatory enzymes, namely, histone acetylases and histone deacetylases (HDACs). Inhibitors of HDAC can modify gene expression in cancer cells in an epigenetic manner (ie, without altering gene sequences) by changing the conformation of DNA, which, in turn, alters gene interaction with transcription factors.

Vorinostat (Zolinza) is an oral HDAC inhibitor that has been shown to increase acetylation of histones and to restore expression of tumor-suppressor and/or cell-cycle regulatory genes—inducing cell-cycle arrest and apoptosis—in a range of cancer cell lines, including cutaneous T-cell lymphoma (CTCL) lines. Vorinostat is currently indicated for the treatment of cutaneous manifestations in patients with CTCL who have progressive, persistent, or recurrent disease during or after treatment with two systemic therapies.¹ The recom-

mended dosage is 400 mg once daily with food. For patients who cannot tolerate this dose, the dosage may be reduced to 300 mg once daily with food and, if necessary, to 300 mg once daily with food for 5 consecutive days a week.

Clinical evidence of efficacy

An update of the open-label phase IIb trial that supported approval of vorinostat in refractory CTCL² was reported at the 2006 Annual Meeting of the American Society of Hematology.³ An additional phase II study that examined twice-daily doses in a similar population was recently reported in the journal *Blood*.⁴

The pivotal phase IIb trial included 74 patients with stage Ib or higher CTCL who had failed to respond to a median of 3 prior systemic therapies (range, 1–12), including bexarotene (Targretin).^{2,3} All patients received vorinostat, 400 mg orally once daily; if necessitated by intolerance, the dose was reduced to 300 mg daily or 300 mg/d for 5 days per week. Pa-

tients had a median age of 61 years; 30 (41%) had Sézary syndrome. The median duration of study treatment was 118 days. Skin disease was assessed using a Severity Weighted Assessment Tool (SWAT), based on the percentage of total body surface involved and the type of lesions (patch, plaque, or tumor) observed.

A positive skin response (defined as a $\geq 50\%$ decrease in SWAT score from nadir) occurred in 22 (30%) of the 74 patients. Among 13 patients with stage IB or IIA disease, 4 (31%) responded to vorinostat.³ Among 61 patients with stage IIB or worse disease, a partial response occurred in 18 (30%), including 10 (33%) of the 30 patients with Sézary syndrome. Although the median time to response was less than 2 months (55 days), in rare cases response to vorinostat required up to 6 months of treatment. The median duration of response was 168 days, and the median time to disease progression (defined as a $> 50\%$ increase in SWAT score from nadir) was 202 days. Response to any prior systemic therapy did not appear to predict the response to vorinostat.

In the other phase II study,⁴ 33 patients who had received a median of five prior therapies for CTCL were assigned, in nonrandom fashion, to treatment with vorinostat, 400 mg once daily (group 1); 300 mg twice daily 3 days/week, followed by an increase to 5 days/week, if tolerated (group 2); or 300 mg twice daily for 14 days, followed by a 7-day rest and

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then 200 mg twice daily thereafter (group 3). Patients had a median age of 67 years; 11 (33%) had Sézary syndrome. The median duration of study treatment was 8 weeks.

Response to vorinostat (defined as $\geq 50\%$ improvement in the baseline Physician's Global Assessment score) occurred in 8 patients (24%) overall. Response was observed in 1 (20%) of 5 patients with a disease stage lower than IIB and in 7 (25%) of 28 patients with stage IIB or higher disease, including 4 (36%) of 11 patients with Sézary syndrome. Changes observed during vorinostat therapy in body surface involvement of CTCL lesions among patients with mycosis fungoides are shown in Figure 1. Response rates by treatment group were 31% (4/13) in group 1, 9% (1/11) in group 2, and 33% (3/9) in group 3. The median time to response and median duration of response were 11.9 weeks (range, 3.6–21.9 weeks) and 15.1 weeks (range, 9.4–19.4 weeks); median time to disease progression was 30.2 weeks. The 300-mg twice-daily regimen had more toxicity without any apparent additional clinical benefit over the 400-mg once-daily regimen.

Toxicities: incidence and management

The most common nonhematologic adverse events observed with vorinostat (400 mg/d) were diarrhea (52%), fatigue (52%), nausea (41%), taste disturbance (28%), anorexia (24%), and weight loss (21%); the most common hematologic toxicities were thrombocytopenia (26%) and anemia (14%).¹ Common laboratory abnormalities included hypercholesterolemia, hypertriglyceridemia, hyperglycemia (69%), an increased serum creatinine level (47%), proteinuria (51%), and electrolyte abnormalities (hypokalemia, hyperkalemia, and hyponatremia). Pulmonary embolism/deep vein thrombosis, QTc interval prolongation, and squamous cell carcinoma have also been reported. Of patients who received the 400-mg

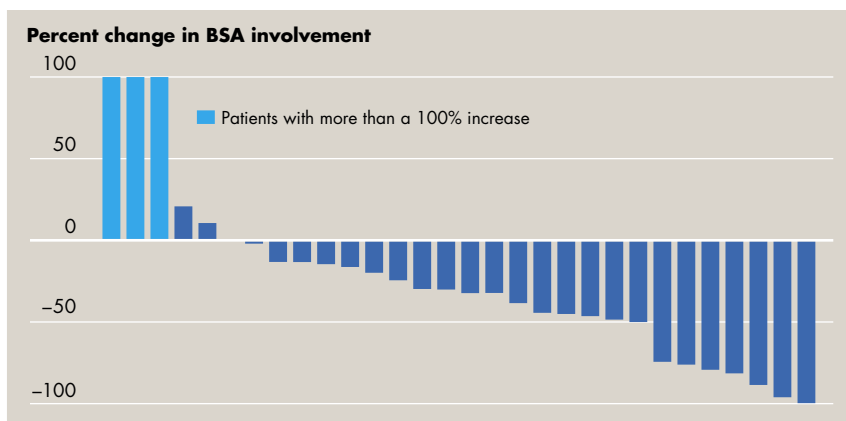


FIGURE 1 Percent change in body surface area (BSA) involvement of cutaneous T-cell lymphoma in patients receiving vorinostat. Adapted, with permission, from Duvic et al.⁴

once-daily dose in both phase II trials, 9% discontinued treatment because of toxicity, and 11% of patients required a dose modification due to adverse events.

Blood cell and platelet counts and serum chemistries (electrolytes, glucose, creatinine) should be monitored every 2 weeks during the first 2 months of treatment with vorinostat and monthly thereafter.¹ An electrocardiogram should be obtained before initiating treatment and repeated periodically during therapy. Vorinostat should be administered with particular caution in patients with congenital long QT syndrome and in patients taking antiarrhythmic agents or other drugs that can lead to QT-wave prolongation.¹

Because of the risk for pulmonary embolism and deep vein thrombosis, patients, particularly those with a history of thromboembolic events, should be monitored for pertinent signs and symptoms. Prolongation of prothrombin time and international normalized ratio have been observed in patients receiving concomitant treatment with warfarin and other coumarin derivatives; careful monitoring is therefore advisable in this setting. Severe thrombocytopenia and gastrointestinal bleeding have been reported with concomitant use of vorinostat and other HDAC inhibitors, such as valproic acid.¹

Antiemetics, antiarrhythmals, and

fluid/electrolyte replacement may be required to prevent dehydration due to gastrointestinal adverse events. Patients should be instructed to drink 2 L of water or other fluids daily for adequate hydration and promptly report excessive vomiting or diarrhea to their healthcare team. Preexisting nausea, vomiting, and diarrhea, as well as hypokalemia or hypomagnesemia, should be adequately controlled prior to initiation of vorinostat therapy.¹

Hyperglycemia has also been observed in vorinostat-treated patients; monitoring of serum glucose is therefore advised, particularly in diabetic or potentially diabetic patients.¹ Some patients may require adjustments in their diet and/or antidiabetic medication.

References

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From the Community Oncologist's Perspective

Treatment options for cutaneous T-cell lymphoma expand

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For many community oncologists in practice, clinical experience with cutaneous T-cell lymphoma (CTCL) is limited to patients encountered during residency and fellowship training and an exceedingly small number of patients treated throughout the course of a career. This number is diminished further by the fact that patients may initially receive therapy from their primary dermatologists and then seek opinions and treatment from referral centers on progression.

Despite these factors, when one does have a chance to treat patients with CTCL, it is gratifying to know that even in this subset of non-Hodgkin's lymphoma—and despite the small number of people affected with this condition—dedicated and intensive research into therapeutic

options has yielded a large number of effective therapies providing significant clinical benefit to patients. In addition, with the significant and often severe physical and emotional morbidities associated with progressive CTCL, despite the lack of a “cure” for this disease, the administration of effective therapies can often lead to a rewarding experience for both the patient and the treating physician.

The results of the two phase II studies of vorinostat (Zolinza) summarized in the accompanying article add another agent to our armamentarium to treat CTCL. The fact that vorinostat yielded responses in patients with heavy pretreatment (at least two prior systemic therapies) makes it a reasonable option for patients previously deemed “re-

fractory” as an alternative to intravenous cytotoxic chemotherapy in this clinical situation.

Where to incorporate vorinostat in the sequence of therapies for CTCL remains somewhat uncertain. Currently available alternative systemic therapies include interferon, bexarotene (Targretin), denileukin diftitox (Ontak), and cytotoxic chemotherapy. It is likely that patients will receive most, if not all, of these agents at some point in their clinical course, but for patient convenience, the use of oral vorinostat may represent a more attractive option than many of the other choices listed above. For now, vorinostat constitutes an important additional treatment for CTCL—the paradigm of converting “progressive” disease into “chronic” disease.

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From the Administrator's Desk

Vorinostat: pharmacoeconomic issues

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As novel medications enter the market, excitement naturally arises. We may suddenly be presented with new options to aid in the ongoing struggle to improve oncologic management. Many times, we find ourselves focused on these rays of sunlight and fail to factor in the cost implications of such a therapy. Vorinostat (Zolinza) certainly fits into this category of extremely promising,

though costly, drugs.

Vorinostat is manufactured by Merck & Co. and is available as 100-mg capsules. The average wholesale price, according to the *Red Book*, is \$8,640 for 120 capsules. Considering an initial dose of 400 mg per day, the average monthly cost would be \$8,640. In terms of cost efficiency, considering an average 30% response rate, the projected cost would

be approximately \$30,000/month per response.

The exorbitant cost of vorinostat must be factored into treatment decisions. Many patients can be left with a significant cost burden, even with insurance coverage. Physicians should be aware of assistance programs that are available and utilize them when possible.

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