

# Leukemia Mortality Linked to Prior Skin Cancer

BY CHARLES BANKHEAD

**PRAGUE** — A prior diagnosis of non-melanoma skin cancer predicts an increased mortality risk in patients with chronic lymphocytic leukemia, investigators from the National Cancer Institute reported.

Overall, chronic lymphocytic leukemia (CLL) patients with a history of nonmelanoma skin cancer had a 30%

greater risk of death, which almost doubled in the subgroup of patients with a prior diagnosis of squamous cell cancer, said Patrick Blake, a medical student at the Cleveland Clinic who is on leave at the NCI.

In one-third of the CLL cases, a diagnosis of nonmelanoma skin cancer preceded the leukemia diagnosis by less than 1 year, increasing to 44% for squamous cell cancer.

“CLL patients with a previous diagnosis of nonmelanoma skin cancer have a significantly decreased survival, compared with CLL patients without nonmelanoma skin cancer,” Mr. Blake and colleagues reported during a poster session at the International Congress of Dermatology.

“Our investigation has unique new findings and expands the findings of two previous studies that found in-

creased mortality among lymphoma patients with a prior history of skin cancer,” he said.

Several case reports have documented incidental identification of subclinical CLL related to excision of squamous cell or basal cell skin cancer. A Scandinavian study of patients with squamous cell skin cancer demonstrated a twofold increased risk of CLL.

Two recent studies documented increased mortality in lymphoma patients with a history of skin cancer. However, investigators in both studies included CLL patients with those who had non-Hodgkin's lymphoma.

To clarify the link between CLL and nonmelanoma skin cancer, NCI investigators analyzed data from a population-

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based study of more than 12,000 cases of CLL diagnosed in Sweden between 1973 and 2003.

Complete medical history was available for the CLL patients, and cause of death was ascertained by data from Sweden's national death registry.

The NCI investigators identified 236 CLL patients with a prior diagnosis of nonmelanoma skin cancer, compared with 11,805 patients with no history of skin cancer.

CLL patients with a history of non-melanoma skin cancer were:

- ▶ Older (78.5 years vs. 71 years);
- ▶ Substantially more likely to be age 70 or older at diagnosis of CLL (80.9% vs. 54.1%);
- ▶ More likely to be male (69.9% vs. 62%);
- ▶ And diagnosed more recently (1993 vs. 1984).

Among the 236 CLL patients with a history of nonmelanoma skin cancer, investigators found that 80 (34%) had a skin cancer diagnosis less than a year before the CLL diagnosis. Of 111 patients with squamous cell skin cancer, 49 (44%) had a skin cancer diagnosis less than a year before the CLL diagnosis.

CLL patients with a prior diagnosis of nonmelanoma skin cancer had a mortality hazard ratio of 1.29, compared with CLL patients who did not have a prior skin cancer diagnosis. In the subgroup of patients who had squamous cell skin cancer, the CLL mortality hazard ratio increased to 1.86. Both of these findings differed significantly from those of the patients with no history of skin cancer ( $P < .0001$ ).

The 5-year survival of CLL patients without a history of skin cancer was 43%, compared with 31% for patients with a history of nonmelanoma skin cancer and 28% for the subgroup with squamous cell cancer ( $P < .0001$ ). ■

## Levulan® Kerastick®

(aminolevulinic acid HCl) for Topical Solution, 20%

For Topical Use Only • Not for Ophthalmic Use

Brief Summary (For full prescribing information, see physician's insert)

### INDICATIONS AND USAGE

The LEVULAN KERASTICK for Topical Solution plus blue light illumination using the BLU-U® Blue Light Photodynamic Therapy Illuminator is indicated for the treatment of minimally to moderately thick actinic keratoses (Grade 1: slightly palpable, better felt than seen or Grade 2: moderately thick, easily seen and felt) of the face or scalp.

### CONTRAINDICATIONS

The LEVULAN KERASTICK for Topical Solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is contraindicated in patients with cutaneous photosensitivity at wavelengths of 400-450 nm, porphyria or known allergies to porphyrins, and in patients with known sensitivity to any of the components of the LEVULAN KERASTICK for Topical Solution.

### WARNINGS

The LEVULAN KERASTICK for Topical Solution contains alcohol and is intended for topical use only. Do not apply to the eyes or to mucous membranes. Excessive irritation may be experienced if this product is applied under occlusion.

### PRECAUTIONS

General: During the time period between the application of LEVULAN KERASTICK Topical Solution and exposure to activating light from the BLU-U Blue Light Photodynamic Therapy Illuminator, the treatment site will become photosensitive. After LEVULAN KERASTICK Topical Solution application, patients should avoid exposure of the photosensitive treatment sites to sunlight or bright indoor light (e.g., examination lamps, operating room lamps, tanning beds, or lights at close proximity) during the period prior to blue light treatment. Exposure may result in a stinging and/or burning sensation and may cause erythema and/or edema of the lesions. Before exposure to sunlight, patients should, therefore, protect treated lesions from the sun by wearing a widebrimmed hat or similar head covering of light-opaque material. Sunscreens will not protect against photosensitivity reactions caused by visible light. It has not been determined if perspiration can spread the LEVULAN KERASTICK Topical Solution outside the treatment site to eye or surrounding skin.

Application of LEVULAN KERASTICK Topical Solution to perilesional areas of photodamaged skin of the face or scalp may result in photosensitization. Upon exposure to activating light from the BLU-U Blue Light Photodynamic Therapy Illuminator, such photosensitized skin may produce a stinging and/or burning sensation and may become erythematous and/or edematous in a manner similar to that of actinic keratoses treated with LEVULAN PDT. Because of the potential for skin to become photosensitized, the LEVULAN KERASTICK for Topical Solution should be used by a qualified health professional to apply drug only to actinic keratoses and not perilesional skin.

The LEVULAN KERASTICK for Topical Solution has not been tested on patients with inherited or acquired coagulation defects.

### Information for Patients:

LEVULAN Photodynamic Therapy for Actinic Keratoses. The first step in LEVULAN KERASTICK photodynamic therapy (PDT) for actinic keratoses is application of the LEVULAN KERASTICK for Topical Solution to actinic keratoses located on the patient's face or scalp. After LEVULAN KERASTICK for Topical Solution is applied to the actinic keratoses in the doctor's office, the patient will be told to return the next day. During this time the actinic keratoses will become sensitive to light (photosensitive). Care should be taken to keep the treated actinic keratoses dry and out of bright light. After LEVULAN KERASTICK Topical Solution is applied, it is important for the patient to wear light-protective clothing, such as a wide-brimmed hat, when exposed to sunlight or sources of light. Fourteen to eighteen hours after application of LEVULAN KERASTICK Topical Solution the patient will return to the doctor's office to receive blue light treatment, which is the second and final step in the treatment. Prior to blue light treatment, the actinic keratoses will be rinsed with tap water. The patient will be given goggles to wear as eye protection during the blue light treatment. The blue light is of low intensity and will not heat the skin. However, during the light treatment, which lasts for approximately 17 minutes, the patient will experience sensations of tingling, stinging, pricking or burning of the treated lesions. These feelings of discomfort should improve at the end of the light treatment. Following treatment, the actinic keratoses and, to some degree, the surrounding skin, will redden, and swelling and scaling may also occur. However, these lesion changes are temporary and should completely resolve by 4 weeks after treatment.

### Photosensitivity

After LEVULAN KERASTICK Topical Solution is applied to the actinic keratoses in the doctor's office, the patient should avoid exposure of the photosensitive actinic keratoses to sunlight or bright indoor light (e.g., from examination lamps, operating room lamps, tanning beds, or lights at close proximity) during the period prior to blue light treatment. If the patient feels stinging and/or burning on the actinic keratoses, exposure to light should be reduced. Before going into sunlight, the patient should protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material. Sunscreens will not protect the patient against photosensitivity reactions.

If for any reason the patient cannot return for blue light treatment during the prescribed period after application of LEVULAN KERASTICK Topical Solution (14 to 18 hours), the patient should call the doctor. The patient should also continue to avoid exposure of the photosensitized lesions to sunlight or prolonged or intense light for at least 40 hours. If stinging and/or burning is noted, exposure to light should be reduced.

**Drug Interactions:** There have been no formal studies of the interaction of LEVULAN KERASTICK for Topical Solution with any other drugs, and no drug-specific interactions were noted during any of the controlled clinical trials. It is, however, possible that concomitant use of other known photosensitizing agents such as griseofulvin, thiazide diuretics, sulfonureas, phenothiazines, sulfonamides and tetracyclines might increase the photosensitivity reaction of actinic keratoses treated with the LEVULAN KERASTICK for Topical Solution.

**Carcinogenesis, Mutagenesis, Impairment to Fertility:** No carcinogenicity testing has been carried out using ALA. No evidence of mutagenic effects was seen in four studies conducted with ALA to evaluate this potential. In the Salmonella-Escherichia coli/mammalian microsome reverse mutation assay (Ames mutagenicity assay), no increases in the number of revertants were observed with any of the tester strains. In the Salmonella-Escherichia coli/mammalian microsome reverse mutation assay in the presence of solar light radiation (Ames mutagenicity assay with light), ALA did not cause an increase in the number of revertants per plate of any of the tester strains in the presence or absence of simulated solar light. In the L5178Y TK± mouse lymphoma forward mutation assay, ALA was evaluated as negative with and without metabolic activation under the study conditions. PpIX formation was not demonstrated in any of these in vitro studies. In the in vivo mouse micronucleus assay, ALA was considered negative under the study exposure conditions. In contrast, at least one report in the literature has noted genotoxic effects in cultured rat hepatocytes after ALA exposure with PpIX formation. Other studies have documented oxidative DNA damage in vivo and in vitro as a result of ALA exposure.

No assessment of effects of ALA HCl on fertility has been performed in laboratory animals. It is unknown what effects systemic exposure to ALA HCl might have on fertility or reproductive function.

**Pregnancy Category C:** Animal reproduction studies have not been conducted with ALA HCl. It is also not known whether LEVULAN KERASTICK Topical Solution can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. LEVULAN KERASTICK Topical Solution should be given to a pregnant woman only if clearly needed.

**Nursing Mothers:** The levels of ALA or its metabolites in the milk of subjects treated with LEVULAN KERASTICK Topical Solution have not been measured. Because many drugs are excreted in human milk, caution should be exercised when LEVULAN KERASTICK Topical Solution is administered to a nursing woman.

### ADVERSE REACTIONS

In Phase 3 studies, no non-cutaneous adverse events were found to be consistently associated with LEVULAN KERASTICK Topical Solution application followed by blue light exposure.

**Photodynamic Therapy Response:** The constellation of transient local symptoms of stinging and/or burning, itching, erythema and edema as a result of LEVULAN KERASTICK Topical Solution plus BLU-U treatment was observed in all clinical studies of LEVULAN KERASTICK for Topical Solution Photodynamic Therapy for actinic keratoses treatment. Stinging and/or burning subsided between 1 minute and 24 hours after the BLU-U Blue Light Photodynamic Therapy Illuminator was turned off, and appeared qualitatively similar to that perceived by patients with erythropoietic protoporphyria upon exposure to sunlight. There was no clear drug dose or light dose dependent change in the incidence or severity of stinging and/or burning.

In two Phase 3 trials, the sensation of stinging and/or burning appeared to reach a plateau at 6 minutes into the treatment. Severe stinging and/or burning at one or more lesions being treated was reported by at least 50% of the patients at some time during treatment. The majority of patients reported that all lesions treated exhibited at least slight stinging and/or burning. Less than 3% of patients discontinued light treatment due to stinging and/or burning.

The most common changes in lesion appearance after LEVULAN KERASTICK for Topical Solution Photodynamic Therapy were erythema and edema. In 99% of active treatment patients, some or all lesions were erythematous shortly after treatment, while in 79% of vehicle treatment patients, some or all lesions were erythematous. In 35% of active treatment patients, some or all lesions were edematous, while no vehicle-treated patients had edematous lesions. Both erythema and edema resolved to baseline or improved by 4 weeks after therapy. LEVULAN KERASTICK Topical Solution application to photodamaged perilesional skin resulted in photosensitization of photodamaged skin and in a photodynamic response. (see Precautions).

**Other Localized Cutaneous Adverse Experiences:** Table 1 depicts the incidence and severity of cutaneous adverse events, stratified by anatomic site treated.

**Adverse Experiences Reported by Body System:** In the Phase 3 studies, 7 patients experienced a serious adverse event. All were deemed remotely or not related to treatment. No clinically significant patterns of clinical laboratory changes were observed for standard serum chemical or hematologic parameters in any of the controlled clinical trials.

TABLE 1 Post-PDT Cutaneous Adverse Events - ALA-018/ALA-019

	FACE		Vehicle (n=41)		SCALP		Vehicle (n=21)	
	LEVULAN (n=139)				LEVULAN (n=42)			
Degree of Severity	Mild/Moderate	Severe	Mild/Moderate	Severe	Mild/Moderate	Severe	Mild/Moderate	Severe
Scaling/Crusting	71%	1%	12%	0%	64%	2%	19%	0%
Pain	1%	0%	0%	0%	0%	0%	0%	0%
Tenderness	1%	0%	0%	0%	2%	0%	0%	0%
Itching	25%	1%	7%	0%	14%	7%	19%	0%
Edema	1%	0%	0%	0%	0%	0%	0%	0%
Ulceration	4%	0%	0%	0%	2%	0%	0%	0%
Bleeding/Hemorrhage	4%	0%	0%	0%	2%	0%	0%	0%
Hypo/hyperpigmentation		22%		20%		36%		33%
Vesiculation	4%	0%	0%	0%	5%	0%	0%	0%
Pustules	4%	0%	0%	0%	0%	0%	0%	0%
Oozing	1%	0%	0%	0%	0%	0%	0%	0%
Dysesthesia	2%	0%	0%	0%	0%	0%	0%	0%
Scabbing	2%	1%	0%	0%	0%	0%	0%	0%
Erosion	14%	1%	0%	0%	2%	0%	0%	0%
Excoriation	1%	0%	0%	0%	0%	0%	0%	0%
Wheal/Flare	7%	1%	0%	0%	2%	0%	0%	0%
Skin disorder NOS	5%	0%	0%	0%	12%	0%	5%	0

### OVERDOSAGE

**LEVULAN KERASTICK Topical Solution Overdose:** LEVULAN KERASTICK Topical Solution overdose have not been reported. In the unlikely event that the drug is ingested, monitoring and supportive care are recommended. The patient should be advised to avoid incidental exposure to intense light sources for at least 40 hours. The consequences of exceeding the recommended topical dosage are unknown.

**BLU-U® Light Overdose:** There is no information on overdose of blue light from the BLU-U Blue Light Photodynamic Therapy Illuminator following LEVULAN KERASTICK Topical Solution application.

### HOW SUPPLIED

The LEVULAN KERASTICK for Topical Solution, 20%, is a single-unit dosage form, supplied in packs of 6. Each LEVULAN KERASTICK for Topical Solution applicator consists of a plastic tube containing two sealed glass ampules and an applicator tip. One ampule contains 1.5 mL of solution vehicle. The other ampule contains 354 mg of aminolevulinic acid HCl. The applicator is covered with a protective cardboard sleeve and cap.

### Product Package

Individual LEVULAN KERASTICK for Topical Solution, 20% 67308-101-01  
Carton of 6 LEVULAN KERASTICKS for Topical Solution, 20% 67308-101-06

### NDC number

Individual LEVULAN KERASTICK for Topical Solution, 20% 67308-101-01  
Carton of 6 LEVULAN KERASTICKS for Topical Solution, 20% 67308-101-06

**Storage Conditions:** Store between 20°–25°C (68°–77°F); excursions permitted to 15°–30°C (59°–86°F) [See USP Controlled Room Temperature]. The LEVULAN KERASTICK for Topical Solution should be used immediately following preparation (dissolution). Solution application must be completed within 2 hours of preparation. An applicator that has been prepared must be discarded 2 hours after mixing (dissolving) and a new LEVULAN KERASTICK for Topical Solution used, if needed.

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