Letter to the Editor

6-Mercaptopurine: An Effective Drug in the Management of Advanced Cutaneous T-Cell Lymphoma

To the Editor:

Although new medications are available for the management of cutaneous T-cell lymphoma (CTCL), many patients and physicians are not satisfied with the results. We previously reported the results in 2 patients with CTCL; one patient was treated for left vocal cord involvement with radiation therapy (photons to 36 Gy), and one patient was treated for base of tongue and vallecula involvement with surgical debridement then radiation with photons (6 MEV [million electron volts] photons) to 40 Gy.[1] Later they received oral 6-mercaptopurine (6-MP) 50 mg alone (patient 1) or with oral allopurinol 300 mg daily for extensive tumor involvment of their skin. Their skin cleared completely for 6 months and more than 3 months, respectively.

In their classic 1972 paper reporting 144 patients with CTCL between 1954 and 1969, Epstein et al[2] noted clinical improvement with a number of chemotherapeutic agents including 2 patients treated with 6-MP. Details concerning dosage, schedule, type of response, and duration were not given. We are unable to find reports of its subsequent use.

We report 3 additional patients treated with oral 6-MP (50 mg daily)/allopurinol (300 mg daily) and provide an update on patients 1 and 4 in the Table. All patients, except patient 5, had stage IV disease at the time of treatment with 6-MP.

In patient 1, the complete response to 6-MP (50 mg daily) was durable for 6 months, and in the following 8 months (dosage between 100–200 mg daily adjusted to keep the absolute neutrophil count above 1000/μL), he was better controlled than during the prior 5 years. The near complete resolution of massive nodal and skin lesions for more than 3 months in patient 2 was impressive, as was the complete resolution of skin nodules and palpable nodes in patient 4 for more than 3 months. Patient 5 did not improve but was treated for less than 2 months with alternate-day oral 6-MP at 50 mg.

Why has 6-MP rarely been used? One reason is the lack of emphasis on results of this therapy in the paper published in 1972.[2] A second reason is the report that 6-MP was inactive in non-Hodgkin lymphoma in the same major study that established its use in leukemia.[3] During the period from 1972 to the present, a number of effective therapies have become available.[4] We conclude that 6-MP is a useful drug in advanced CTCL and deserves additional study in these patients. It is an easily administered oral medication that also is inexpensive; the cash price of a month's supply of 6-MP (50 mg daily) and allopurinol (300 mg daily) at our center is approximately $23. We used 6-MP with allopurinol because the latter may have effects other than inhibiting degradation of 6-MP.[5] In her reply to a question regarding this combination, the drug's codiscoverer, Gertrude Elion, noted that in mice the combination of 6-MP and allopurinol had a higher therapeutic index than 6-MP alone.[6]

Hematopoietic toxicity is monitored with complete blood cell counts and the drug held or dose decreased for absolute neutrophil count below 1000/μL.[7] Hepatic toxicity, commonly reversible cholestatic jaundice, is monitored with bilirubin and hepatic enzyme levels; hepatic necrosis and veno-occlusive diseases are rare. 6-Mercaptopurine is teratogenic and immunosuppressive. Because absence of the enzyme thiopurine methyltransferase markedly increases myelosuppression, it is now recommended that it be measured before therapy.[7]

Sincerely,

Wade K. Smith, MD
W. Kenneth Blaylock, MD

From Virginia Commonwealth University, School of Medicine, Richmond. Dr. Smith is from the Division of Hematology/Oncology, Department of Medicine. Dr. Blaylock is from the Department of Dermatology.

The authors report no conflict of interest.

Patients With CTCL Treated With 6-MP

Patient No.	Age, y/ Gender	Stage at Diagnosis/Year	Stage at 6-MP/Year	Prior Treatment/No.[a]	Extent of Disease Prior to Treatment With 6-MP	Response	Subsequent Course
1	49/M	IB/1981	IVB/2002	a, b, c, d, e, g (EPOCH); prednisone pulses/11+	Left vocal cord (CR to 36 Gy photon radiation); extensive skin tumors with ulceration; repeated pneumonia[b]	Skin CR for 6 mo and limited lesions for an additional 8 mo	Died in February 2004 with massive skin involvement
2	37/M	IVB/2002	IVB/2002	b, c, e/3	Large masses of nodes >20 cm in axilla and neck (both bilateral); mass right thumb with bony erosion; extensive massive skin nodules; prior response of bilateral inguinal nodes to radiation therapy elsewhere	Dramatic, rapid, and marked reduction in nodes, skin tumors, and resolution of thumb lesion for >3 mo	Rapid explosive growth of abdominal nodes, only partially responsive to EPOCH for a few weeks; then progression and involvement of liver and fatal obstructive renal failure
3	30/F	Unknown/1999	IVB/2002	a, b, f, g (CHOP ×6)/5	Initial patch and plaques treated elsewhere; by 1999 had dyspnea on exertion and suspected interstitial lung involvement, first biopsied (+) in 2002; small skin nodules, patches, and plaques	Partial skin response for 8 mo but interstitial involvement gradually worsened	Responded to gemcitabine and after relapse has responded to interferon alfa and light treatment of skin for >3 y; alive
4	48/M	IIB/2003	IVB/2004	a, b, f, g/4	Skin tumors and enlarged peripheral nodes (not biopsied) in 2004; developed base of tongue and vallecula involvement treated with debridement and XRT (6 MEV photons to 40 Gy); line sepsis[b]	Skin CR for >3 mo	Distal tibial lesion (open bone biopsy + for CTCL) treated with XRT; repeated pneumonia/possible lung and mediastinal/hilar nodes (supported with antibiotics and IV immunoglobulin); sent home with hospice in July 2005 and is presumed dead
5	83/F	IIB/2001	IIB/2005	a, b, c, e/7	Plaques involving most of body surface	No improvement in skin over 2 mo	TSEB but poor response; died in February 2006

Abbreviations: CTCL, cutaneous T-cell lymphoma; 6-MP, 6-mercaptopurine; M, male; EPOCH, combination chemotherapy with etoposide, prednisone, oncovin, cyclophosphamide, doxorubicin; CR, complete response; F, female; CHOP, combination chemotherapy with cyclophosphamide, hydroxyldaunorubicin, oncovin, prednisone; XRT, radiation with photons; MEV, million electron volts; IV, intravenous; TSEB, total skin electron beam.

[a]Prior treatments included the following: a=topical retinoids and/or steroids/topical nitrogen mustard; b=photons or TSEB; c=light, psoralen plus UVA, or extracorporeal photophoresis; d=subcutaneous interferon alfa; e=single-agent chemotherapy (oral weekly methotrexate, pentostatin, gemcitabine); f=denileukin difitox; g=multiagent chemotherapy.

[b]Reported by Reiter et al.[1]

REFERENCES

1. Reiter ER, Lynch JM, Smith WK. Extracutaneous manifestations of mycosis fungoides in the head and neck. Poster presented at: The Triological Society Southern Section Meeting; January 2005; Miami, FL.
2. Epstein EH Jr, Levin DL, Croft JD Jr, et al. Mycosis fungoides. survival, prognostic features, response to therapy, and autopsy findings. *Medicine (Baltimore)*. 1972;51:61-72.
3. Burchenal JH, Murphy ML, Ellison RR, et al. Clinical evaluation of a new antimetabolite, 6-mercaptopurine, in the treatment of leukemia and allied diseases. *Blood*. 1953;8:965-999.
4. Duvic M, Foss FM. Mycosis fungoides: pathophysiology and emerging therapies. *Semin Oncol*. 2007;34(6, suppl 5): S21-S28.
5. Elion GB, Callahan S, Nathan H, et al. Potentiation by inhibition of drug degradation: 6-substituted purines and xanthine oxidase. *Biochem Pharmacol*. 1963;12:85-93.
6. Elion GB. Symposium on immunosuppressive drugs. biochemistry and pharmacology of purine analogues. *Fed Proc*. 1967;26:898-904.
7. Hande KR. Principles and pharmacology of chemotherapy. In: Greer JP, Foerster J, Rodgers GM, et al, eds. *Wintrobe's Clinical Hematology*. 12th ed. Philadelphia, PA: Wolters Kuwer/Lippincott Williams & Wilkins; 2009:1694-1720.

Letter to the Editor

CONTINUED FROM PAGE 218

Comment

Triple EMPD was reported in a Japanese patient in 1971,[2] and it continues to be extremely rare outside of Japan.[1-5] Although the reason for its rarity outside of Japan is unclear, it may indicate a genetic predisposition to or an increased national awareness of this unusual presentation of the disease.

Triple EMPD most commonly involves the groin and axillary regions. Some patients with triple EMPD have inconspicuous axillary involvement, as in our case, or even subclinical involvement, despite histologic evidence of disease. In Japan, the axillary regions of patients with EMPD are meticulously examined and often routinely biopsied, even in the absence of clinical findings.[3]

The pathogenesis of multiple EMPD is unknown. It may be due to an oncogenic stimulus that acts on vulnerable cells in the epidermis in multiple areas of the body. Given a pronounced predominance of this disease in males,[3,4] androgens also may play a role.

Clinicians should be aware of the potential for multiple EMPD and carefully examine, if not biopsy, the axillary regions of patients with genital EMPD. Because axillary lesions may develop after genital lesions,[4] close follow-up is essential. Fortunately, axillary tumors rarely are invasive and have not been reported to metastasize.[4,5]

Sincerely,
Christine C. Tam, MD
Phillip S. Ragland, MD
Allan C. Harrington, MD

Dr. Tam is from the Dermatology Office of David Spott, MD, Clinton, Maryland. Dr. Ragland is from Anne Arundel Dermatology, Annapolis, Maryland. Dr. Harrington is from the Department of Dermatology, Johns Hopkins University, Baltimore, Maryland.

The authors report no conflict of interest.

REFERENCES

1. Hatta N, Yamada M, Hirano T, et al. Extramammary Paget's disease: treatment, prognostic factors and outcome in 76 patients [published online ahead of print November 19, 2007]. *Br J Dermatol*. 2008;158:313-318.
2. Kawatsu T, Miki Y. Triple extramammary Paget's disease. *Arch Dermatol*. 1971;104:316-319.
3. Kitajima S, Yamamoto K, Tsuji T, et al. Triple extramammary Paget's disease. *Dermatol Surg*. 1997;23:1035-1038.
4. Koseki S, Mitsuhashi Y, Yoshikawa K, et al. A case of triple extramammary Paget's disease. *J Dermatol*. 1997;24:535-538.
5. Abe S, Kabashima K, Nishio D, et al. Quadruple extramammary Paget's disease. *Acta Derm Venereol*. 2007;87:80-81.
6. Van Hamme C, Marot L, Dachelet C, et al. Paget's extramammary disease of the axillae and perineum [in French]. *Ann Dermatol Venereol*. 2002;129(5, pt 1):717-719.