Commentary and update: Topical chemotherapy with mechlorethamine for mycosis fungoides[1]

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Historical perspectives

During World War I, Krumbharr and Krumbharr[1] observed that fatal poisoning from exposure to war gas often was accompanied by severe leukopenia and bone marrow aplasia. Shortly thereafter, Pappenheimer and Vance[2] demonstrated in animals that the cytotoxic effect of war gas on hematopoietic tissues was due to the sulfur mustard (dichlorodiethyl sulfide) component. After the war, Adair and Bagg[3] utilized the local destructive effects of sulfur mustard solutions on tissue to treat a variety of cutaneous tumors, but their observations were ignored.

With the advent of World War II, research on war gases was resumed and a series of nitrogenous analogs of sulfur mustard (the nitrogen mustards) were developed as potential offensive weapons. It soon was recognized that sulfur and nitrogen mustards share the systemic cytotoxic effects following absorption and that cellular susceptibility to these agents seemed to be related in a general way to the degree of proliferative activity of tissues.[4] This observation suggested that the nitrogen mustards may be potentially valuable for treatment of malignant disease, and in clinical trials beginning in 1942, one of the nitrogen mustards bis (β-chloroethyl)methylamine (also known as mechlorethamine or HN2) was demonstrated to have a beneficial influence on a variety of lymphoid neoplasms.[4,5] Five years later, HN2 was administered for the palliative systemic therapy of advanced mycosis fungoides lymphoma (MF).[6,7]

This commentary salutes the pioneering work of Haserick et al[8] who in 1959 were the first investigators in this country to demonstrate that topical application of HN2 solution causes regression of MF lesions. Subsequently, Madison and Haserick[9] reported short-term results with topical HN2 chemotherapy in 8 additional cases of MF and a variety of other benign and malignant dermatoses. Their method of treatment consisted of painting lesional skin with 20 mg/dl solutions of HN2 (10 mg/50 ml water) once daily for four days. Even short courses of treatment of topically applied HN2 usually cleared patches and plaques, but not frank tumors or the erythroderma of Sézary syndrome, and the most common adverse reaction was allergic contact dermatitis. Unknown to these authors, similar observations had been reported in the Hungarian literature by Sipos and Jáksó in 1956.[10]

After these initial investigations, Van Scott and Kalmanson[11] and Van Scott and others[12,13] demonstrated that topical HN2 solutions could be administered daily to the entire skin surface for long intervals (years) without systemic toxicity from percutaneous absorption, even at higher concentrations (40 mg/dl) than currently advocated. Since then, the usefulness of topical HN2 chemotherapy has been confirmed by several other groups not only for MF,[14–17] but also for other conditions such as psoriasis,[18–22] histiocytosis X,[23–26] multicentric reticulohistiocytosis,[27] and actinic reticuloid.[28]

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Mechanism of action

In aqueous solutions, HN2 undergoes intramolecular cyclization in each of its two side chains to form highly reactive ethylenimonium ion intermediates capable of forming strong covalent bonds (alkylation) with various nucleophilic molecular groups.[29,30] In tissues, a large number of biologically important compounds react with ionic HN2,[31,32] but probably the most important biologically is the reaction with guanine and other base residues in the DNA molecule. Since HN2 is a bifunctional alkylating agent, crosslinks are formed between interstrands of DNA and DNA-nucleoproteins,[33–35] thereby interfering with normal mitoses and cell division. Moreover, the reaction of HN2 with DNA appears to account for the mutagenic and carcinogenic properties associated with this drug.[36,37]

Because of the effect on DNA, the cytotoxicity of systemically administered HN2 generally becomes manifest first in rapidly proliferating tissues.[4] However, the lethal effect of HN2 on lymphocytes, which normally have a low rate of proliferation and yet are quite sensitive to HN2, depends on other, poorly understood, cytotoxic mechanisms. The different sensitivities of cells to HN2 presumably underlie the therapeutic effectiveness observed in diverse conditions such as psoriasis (antiproliferative action on hyperkinetic epithelium) and MF (exquisite sensitivity of neoplastic lymphocytes). However, it is conceivable that some of the action of topical HN2 on MF may be mediated indirectly, perhaps via interference with the interactions between epidermal cells, Langerhans cells, and neoplastic T-lymphocytes in the skin[38,39] or via clinically inapparent immunostimulatory mechanisms.[14]

Role of topical HN2 chemotherapy in the management of MF

MF is a progressive malignant lymphoma characterized by the proliferation of atypical T-lymphocytes that preferentially infiltrate the skin.[40,41] The median survival is about 5 years after histopathologic diagnosis although this varies greatly from patient to patient. The major prognostic determinant for patients with MF is the extent (stage) of disease as defined by a tumor-node-metastasis (TNM) classification scheme.[42]

The likelihood of a complete regression of a lesion from topically applied HN2 depends on the magnitude of cutaneous infiltration at the lesion site.[9–11] For this reason, topical HN2 chemotherapy by itself is indicated primarily for patients with relatively early (pretumorous) intracutaneous MF. Our experience with large numbers of such patients indicates that about 80% will achieve a complete clinical and histologic response.[12,13] Occasionally, some patients with erythrodermic MF (no Sézary cells in the blood) or highly responsive tumor-phase MF also will clear with topical HN2 applications alone without supplemental treatments. Furthermore, continued administration of HN2 will maintain the disease-free status in about half of these patients for prolonged intervals even though the disease may not be eradicated permanently (cured) in many instances.[13]

The main acute adverse reactions limiting the use of topical HN2 chemotherapy in MF are allergic sensitization of the delayed type (about 40% of patients) and cutaneous irritation (about 10% of patients).[12] In addition, prolonged topical use of HN2 is associated with an increased frequency of epithelial neoplasms (squamous cell carcinomas, keratoacanthomas) mostly on sun-exposed areas and genital skin.[43–45] There has been no apparent increase in the frequency of malignant melanomas or internal malignancies.

Since topical HN2 chemotherapy is free of toxic systemic effects, it also is a valuable adjunct therapy for patients with advanced MF being treated primarily with other therapies. In our experience, systemically administered drugs often influence cutaneous disease to a lesser degree than extracutaneous disease, as if the skin was a sanctuary from the drugs. For this reason, it is quite useful to add topical HN2 to a systemic chemotherapy regimen. Moreover, several investigators have utilized topical HN2 chemotherapy in MF to prolong the duration of complete responses after electron beam radiotherapy[46] and to augment the responses from methoxsalen photochemotherapy.[47]

Although intensive topical HN2 chemotherapy can produce an apparent disease-free state for prolonged intervals of time, it has not been clearly shown that such treatment substantially alters the natural course of disease, resulting in improved survival. Since a randomized study involving untreated patients cannot be performed because of medical and ethical considerations, the answers must be inferred by comparing results achieved in patients treated with topical HN2, with historical controls, and with other modalities.

Historically, MF has been considered to be a relentlessly progressive disease that almost always proved to be fatal.[48] In a large series of patients studied at the National Institutes of Health (NIH) between 1954 and 1969, Epstein et al[49] found that patients presenting *without* cutaneous tumors, ulcers, or palpably enlarged lymph nodes had a median survival of about 8 years after biopsy diagnosis. Our experience at Temple University with a similar group of patients treated primarily with topical HN2 chemotherapy since 1968 indicates a much longer median survival time (greater than 10 years), even if patients with tumor phase intracutaneous disease are included in the analysis.[13] These data suggest that topical HN2 chemotherapy has a beneficial influence on the course of disease. However, no definite conclusions can be made because it is quite possible that the NIH series included patients with delayed histopathologic diagnosis or with inherently more aggressive disease.

Another method of evaluating the impact of topical HN2 chemotherapy on MF is comparing therapeutic results achieved with total-skin electron-beam radiotherapy (TSEB). Because TSEB has been demonstrated to have curative potential for early intracutaneous MF,[50,51] it perhaps is significant that one retrospective[13] and one prospective[17] study comparing these two treatments suggest a comparable effect on survival even though the actuality of cure undoubtedly occurs less frequently with topical HN2 chemotherapy. Therefore, it seems reasonable to conclude that the improved outlook for patients with MF is related to the control of cutaneous lesions, which in turn may decrease the potential for extracutaneous involvement, inhibit the emergence of more malignant clones of tumor cells, and/or reduce the chance of ulcerations and life-threatening infections.

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