STUDY

A Prospective Study of Cutaneous Intolerance to Topical Mechlorethamine Therapy in Patients With Cutaneous T-Cell Lymphomas

Eric Estève, MD; Martine Bagot, MD, PhD; Pascal Joly, MD, PhD; Pierre Souteyrand, MD, PhD; Marie Beylot-Barry, MD; Loic Vaillant, MD, PhD; Michèle Delaunay, MD; Marie Françoise Avril, MD; Liliane Laroche, MD, PhD; Florent Grange, MD; Elisabeth Thomine, MD; Janine Wechsler, MD, PhD; for the French Study Group of Cutaneous Lymphomas

Objective: To study the exact frequency and the histological features of cutaneous intolerance to mechlorethamine (CIM) hydrochloride therapy in patients with cutaneous T-cell lymphomas, including Langerhans cell histiocytosis.

Design: A multicenter prospective study was conducted from January 1, 1994, to May 31, 1996, in 12 different hospitals in France.

Patients: Of the 52 patients with cutaneous T-cell lymphomas or Langerhans cell histiocytosis, 35 were men and 17 were women, aged 18 to 87 years. Of the 52 patients, 35 had mycosis fungoides, 8 had nonepidermotropic cutaneous lymphoma, 7 had lymphomatoid papulosis, 1 had Sézary syndrome, and 1 had Langerhans cell histiocytosis.

Methods: Patients were treated with topical applications of a 0.02% aqueous solution of mechlorethamine. The diagnosis of CIM was determined by the presence of erythema and pruritus. Patients who developed CIM underwent closed patch testing with three 10-fold dilutions of 0.02% mechlorethamine solution. A positive patch test result was the presence of erythema and pruritus, a weak result was the presence of simple erythema without pruritus, and a negative result was the absence of erythema and pruritus. Skin biopsy specimens from patients with positive patch test results were obtained in patients who developed CIM. The biopsy specimens were reviewed, and the results determined by 2 pathologists (E.T. and J.W.). The histopathological findings were classified in 3 categories: (1) spongiotic dermatitis, (2) irritant dermatitis, and (3) insignificant or normal. In September 1998, the referring physicians were contacted if mechlorethamine therapy had been continued in patients with CIM.

Results: Of the 52 patients, 43 were evaluated for tolerance to mechlorethamine therapy. Of the 43 patients, CIM developed in 23, from 4 days to 9 months after the initiation of mechlorethamine therapy. Of those 23 patients, CIM developed within 3 months in 21 and within 1 month in 13. Closed patch tests were performed in 21 of the 23 patients who developed CIM. The results of the patch test were positive in 12, weak in 4, and negative in 5. Of these 21 patients, 14 skin biopsy specimens were obtained in 14 different patients who had positive or weak patch test results. The specimens showed histological features that were consistent with spongiotic dermatitis in 9 patients, irritant dermatitis in 2, and insignificant or normal in 3. All 9 patients with histological features of spongiotic dermatitis discontinued mechlorethamine therapy. All 5 patients without histological features of spongiotic dermatitis were able to resume mechlorethamine therapy. These results do not correlate with those of previous study results.

Conclusions: Mechlorethamine therapy is a cost-effective and easily administered treatment for cutaneous T-cell lymphomas. Our study shows that allergic dermatitis caused by mechlorethamine therapy is an early and frequent adverse reaction in patients with cutaneous T-cell lymphomas. The most common histological feature of patients with CIM is spongiotic dermatitis.

Arch Dermatol. 1999;135:1349-1353

The affiliations of the authors and the members of the French Study Group of Cutaneous Lymphomas appear in the acknowledgment section at the end of the article.

MYCOSIS fungoides (MF) is a well-defined subset of cutaneous T-cell lymphomas (CTCLs). The most common initial manifestations of MF are patches and plaques on the skin.[1] Initial treatments include topical mechlorethamine hydrochloride, topical carmustine, topical corticosteroids, psoralen–UV-A (PUVA), UV-B radiation, and total skin electron beam radiation.[2-5] Topical mechlorethamine therapy is a convenient and effective treatment, especially for elderly patients who can easily prepare it at home. It can be safely administered for prolonged periods without systemic toxic effects. The major adverse reaction is allergic dermatitis or irritant dermatitis, which can necessitate discontinuation of mechlorethamine therapy. Cutaneous intolerance to mechlorethamine (CIM) therapy appears in 30% to 80% of patients with CTCL.[6-16] The distinction between a simple

PATIENTS AND METHODS

Fifty-two patients from 12 different hospitals in France were included in the prospective study conducted from January 1, 1994, to May 31, 1996. Of the 52 patients, 35 were men and 17 were women. The mean (SD) age was 58 (7) years with a range of 18 to 87 years. The inclusion criteria were the following: (1) CTCL or Langerhans cell histiocytosis requiring topical mechlorethamine therapy; (2) regular follow-up every month or every 2 months by the assigned dermatologist; (3) treatment with topical mechlorethamine without PUVA therapy; and (4) local or general corticosteroids administered within 15 days before starting mechlorethamine therapy. The stages of CTCL were not recorded. The following skin diseases were diagnosed in the 52 patients: MF (35), nonepidermotropic cutaneous lymphoma (8), lymphomatoid papulosis (7), Sézary syndrome (1), and Langerhans cell histiocytosis (1). Mechlorethamine powder was diluted in water and applied locally every day or every other day. The usual concentration was 0.02% (10 mg/50 mL) solution (Carylolysine; Laboratories Synthélabo, Meudon LaForet, France). The assigned physician clinically examined the patients every month or every 2 months for signs of erythema, pruritus, and dryness of the skin in contact with mechlorethamine. The diagnosis of CIM was determined by the presence of erythema and pruritus. Allergological evaluation was required for every case of CIM. Closed patch tests were prepared using a 0.02% aqueous solution of mechlorethamine at the following 3 dilutions: 10-fold, 100-fold, and 1000-fold. The patch test sites were examined 48 or 78 hours after application, and the results were determined using the International Contact Dermatitis Research Group standardization criteria.[17] A positive patch test result was the presence of erythema and pruritus, a weak result was the presence of simple erythema without pruritus, and a negative result was the absence of erythema and pruritus. Skin biopsy specimens were obtained at all positive patch test reaction sites only and with the consent of the patient. All histological slides were reviewed independently by 2 pathologists (E.T. and J.W.), who were blinded to the clinical aspect of each patient. Litigious cases were reviewed on a multihead microscope and the results agreed on by consensus. The histopathological findings were classified in 3 categories: (1) spongiotic dermatitis, defined by spongiosis and superficial lymphohistiocytic infiltrates; (2) irritant dermatitis, defined by lack of spongiosis, presence of epidermal ulceration, or necrosis with polymorphous superficial and deep infiltrates; and (3) nonspecific dermatitis (insignificant or normal aspect), defined by lack of epidermal changes and presence of discrete lymphohistiocytic infiltrates.

In September 1998, the referring physicians of this study were contacted if mechlorethamine therapy had been continued in patients with CIM.

irritant dermatitis and allergic dermatitis may be clinically difficult to determine. Therefore, we conducted a prospective study to evaluate the frequency of irritant dermatitis and allergic dermatitis using patch testing and histological analysis in patients with CIM.

RESULTS

Within the first month of follow-up, 2 patients died, 5 patients were lost to follow-up, and 2 patients discontinued mechlorethamine therapy for reasons other than CIM. These 9 patients were excluded from analysis. The remaining 43 patients had complete follow-up data, and they were evaluated for tolerance to mechlorethamine use. Of the 43 patients, 23 (14 men and 9 women), aged 20 to 75 years (mean [SD], 53 [9] years), developed CIM 4 days to 9 months after the initiation of mechlorethamine therapy (mean [SD], 1 [6] month). Of the 23 patients, CIM occurred within the first month in 13 and within 3 months in 21. Of the 23 patients, 15 had MF, 5 had lymphomatoid papulosis, 2 had nonepidermotropic cutaneous lymphoma, and 1 had Langerhans cell histiocytosis. Closed patch tests were performed in 21 of the 23 patients (2 of the 23 patients were excluded for technical reasons). The results of the 21 patch tests were positive in 12, weak in 4, and negative in 5. The results of further patch testing using 3 dilutions of mechlorethamine for the 12 patients are presented in the **Table**. Of the 21 patients, 14 biopsy specimens were obtained from 14 different patients with positive or weak patch test results. The biopsy specimens were reviewed by 2 pathologists (E.T. and J.W.). Of the 14 biopsy specimens, the histological features were consistent with spongiotic dermatitis in 9, irritant dermatitis in 2, and insignificant or normal in 3. Of the 23 patients with CIM, 1 man had received prior total skin electron beam radiation therapy and had a negative patch test result; 1 woman had had a previous intolerance to carmustine and 1 woman had previously received mechlorethamine therapy without developing CIM: both women had positive patch test results with histological features of spongiotic dermatitis. Of the 20 patients without CIM, no one received previous treatment with mechlorethamine, carmustine, or total skin electron beam radiation.

Of the 23 patients with CIM, 12 resumed topical mechlorethamine therapy after resolution of CIM. Patients resumed mechlorethamine therapy by initially using lower concentrations and then slowly increasing the concentration until a tolerable dose was sustained. The initial concentrations varied among the centers (10 mg/50 mL to 10 mg/1000 mL). Of these 12 patients, 4 had histological features of spongiotic dermatitis and all 4 discontinued mechlorethamine therapy because they developed CIM, despite the use of higher dilutions of mechlorethamine, and/or the use of local corticosteroids, and/or PUVA therapy. The 8 remaining patients without histological features of spongiotic dermatitis were able to resume sustained applications with the use of progressive dilutions of mechlorethamine. The patch test reults of these 8 patients were negative in 2, weak in 1, positive in 4, and 1 did not undergo patch testing. Of the 4 with positive patch test results, 1 did not undergo a biopsy, 2 had biopsy specimens showing

histological features of irritant dermatitis, and 1 had a biopsy specimen showing normal or insignificant histological features. Comparing the groups with and without histological features of spongiotic dermatitis using the Fisher exact test showed a statistically significant difference ($P = .002$).

COMMENT

Our study confirms that CIM is a frequent adverse reaction to topical mechlorethamine therapy. It is a cutaneous reaction that appeared early, within the first 3 months of treatment, in 21 (91%) of the 23 patients in our study. In 9 (64%) of the 14 skin biopsy specimens, the histological result was spongiotic dermatitis. This result is of interest because we did not find any previous large studies[6-12] with comparable results in patients who had CTCL with tolerance to mechlorethamine therapy, in addition to patch testing, biopsy specimens of patch testing, and systematic review of the skin biopsy specimens. Waldorf et al[13] reported biopsy results from 3 patients with MF receiving mechlorethamine therapy who underwent patch testing using mechlorethamine, and all 3 developed spongiotic dermatitis.

Mycosis fungoides is a well-defined subtype of CTCL, and the symptoms of patients with patches and plaques may not respond to certain therapies.[1] Initial treatments for these patients include topical mechlorethamine, topical carmustine, topical corticosteroids, PUVA, UV-B radiation, and total skin electron beam radiation therapies. All are effective in treating MF[1-3,6,14,16,18-21]; however, because topical mechlorethamine can be easily prepared at home, it is frequently used, especially in elderly patients, in France.

Mechlorethamine is a nitrogen mustard that was introduced in the medical field approximately 50 years ago to treat CTCL.[19,20] It is one of the safest therapies currently used to treat the early stage of MF. It is used as a 0.02% dilution of an aqueous solution, which has been shown to have an acceptable therapeutic risk-benefit ratio. The major adverse reactions to mechlorethamine therapy are cutaneous reactions. Short-term adverse reactions include pruritus, xerosis, hyperpigmentation, and less commonly urticaria, bullous reactions, and Stevens-Johnson syndrome.[3,7,22-24] The most common adverse reaction is CIM, defined by erythema and pruritus at the site of application.[1-3] In our study, 23 (53%) of the 43 patients developed CIM; this percentage is similar to those reported in the literature.[14,18,19] In several previous studies,[2,6,8,9,12,18] the frequencies of CIM in patients were 38%, 49%, 57%, 58%, 70%, and 83%. The mean (SD) age (53 [9] years) of patients with CIM in our study was similar to those of a previous study[19] (58 [7] years) and does not seem to be a prognostic factor in the development of CIM. Of the 23 patients with CIM in our study, CIM occurred within the first month of treatment with mechlorethamine in 13 (56%) and within 3 months in 21 (91%). These data are similar to that of previous reports[6,7,9,11,19] that CIM usually occurs in the first weeks of mechlorethamine treatment.

Because the distinction between a simple irritant dermatitis and an allergic dermatitis can be clinically difficult to determine in patients with erythema and pruritus due to CTCL, we systematically obtained biopsy specimens only from the patch test sites. In our study, 21 of the 23 patients received closed patch tests. Of the 21 patients, 14 with positive or weak results had biopsy specimens that were analyzed. Almost half of our patients (9 of 23) who developed CIM exhibited both pruritus and erythema, sensitization to mechlorethamine therapy, positive patch test results, and histological features of spongiotic dermatitis. Results reported by Waldorf et al[13] of 3 biopsy specimens removed from patients with positive patch test results showed spongiotic dermatitis with vesiculation, dermal edema, and perivascular infiltrate of lymphocytes. Therefore, we conclude that spongiotic dermatitis is the most frequent histological pattern in patients who develop CIM.

In patients with spongiotic dermatitis, it is still not clearly defined whether mechlorethamine therapy should be discontinued, and the best therapeutic schedule for mechlorethamine therapy remains unclear. Recent studies[2,8-12,15] have proposed various methods to prevent allergic sensitization to mechlorethamine therapy. Most of these methods were not effective and may have caused severe adverse reactions.[10] In all the studies above, the diagnosis of hypersensitivity to mechlorethamine was based on clinical grounds; therefore, it is difficult to determine the proportion of actual diagnoses of spongiotic dermatitis to that of mechlorethamine use. In patients with psoriasis, it has been shown that intravenous desensitization to mechlorethamine is unsuccessful.[10] Therapy with UV-A or UV-B can reduce the incidence of allergic contact dermatitis caused by mechlorethamine therapy[11] and delays contact sensitization to mechlorethamine.[12] In patients with MF, there is no clear evidence that the use of PUVA therapy delays the development of mechlorethamine sensitization.[7,9] The effectiveness of desensitization using intravenous injection of mechlorethamine in patients remains controversial. In 1977, Leshaw et al[8] found the same sensitization rate (38%) comparing 2 groups of 13 patients with MF,

Patch Test Results in 12 Patients With Cutaneous T-Cell Lymphomas

Patient No.	Type of Cutaneous Lymphoma	Dilutions of Mechlorethamine*		
		10-Fold	100-Fold	1000-Fold
1	Lymphomatoid papulosis	+	–	–
2	Nonepidermotropic cutaneous lymphoma	+	–	–
3	Mycosis fungoides	–	–	–
4	Mycosis fungoides	+	–	–
5	Mycosis fungoides	–	–	–
6	Lymphomatoid papulosis	–	–	–
7	Lymphomatoid papulosis	–	–	–
8	Mycosis fungoides	+	–	–
9	Lymphomatoid papulosis	–	–	–
10	Langerhans cell histiocytosis	–	–	–
11	Mycosis fungoides	+	–	–
12	Mycosis fungoides	+	+	+

**The plus sign indicates a positive result, which was the presence of pruritus and erythema; the minus sign, a negative result, which was the absence of erythema and pruritus. All patients had positive patch test results to the usual concentration of 0.02% mechlorethamine solution.*

with or without tolerogenic injections. To our knowledge, the largest series was by Vonderheid et al[6] in 1977. In this study, of 60 patients who had MF and CIM, 31 underwent intravenous desensitization to mechlorethamine and 17 of the 31 were able to resume topical mechlorethamine therapy. Nevertheless, 7 patients developed local cutaneous reactions requiring extended hospitalization, and all 31 patients in the study were hospitalized because of this treatment.[6] Because of the inconvenience to the patient, this method has been largely abandoned. In addition, the use of mechlorethamine ointment to reduce the frequency of CIM also has been proposed by Price et al.[18,20] In one study,[18] only 3 of the 12 patients with a history of CIM developed contact dermatitis and none of the patients who were exposed for the first time to mechlorethamine developed CIM. Price et al[18] hypothesize that patients with hypersensitivity to the aqueous solution of mechlorethamine have developed sensitivity to components produced from the breakdown of the product while in solution and that the ointment preparation may preserve the mechlorethamine molecule in its original state.[18-20,25] Nevertheless, the French and the American preparations of mechlorethamine are different and it is not technically possible to mix the French mechlorethamine in an anhydrous vehicle.[26] The use of mechlorethamine ointment has not been officially recommended for use in France, and, currently, the aqueous solution is the only form that may be used to treat patients with cutaneous disorders.[14,26]

Local desensitization with a diluted aqueous solution of mechlorethamine in patients with MF was shown to be useful by Constantine et al[15] and Ramsay et al,[2] but in these 2 studies, the authors diagnosed patients as having CIM based only on clinical findings. The authors administered to patients aqueous solutions of mechlorethamine with dilutions between 10 mg/1200 mL to 10 mg/1800 mL every day for 1 week. If the dilution was tolerated, the dosage could be approximately doubled the following week until a tolerable dosage was achieved or the original concentration was tolerated. Using this method, 71 of the 73 patients were able to tolerate sustained applications of mechlorethamine in the 2 studies. Our results do not support the results of these 2 studies because only 4 of the 9 patients with histological features of spongiotic dermatitis were unable to tolerate the mechlorethamine treatment despite the use of progressive dilutions, local corticosteroids, and/or PUVA therapy. An explanation for the tolerance to mechlorethamine use mentioned in the studies above could be the application of lower dilutions of mechlorethamine (10 mg/50 mL to 10 mg/1000 mL) or a chemical difference between the aqueous form of mechlorethamine used in France and the ointment used in studies conducted in the United States. The new challenge of mechlorethamine in our study was retrospective. Further investigation is necessary to arrive at an exact analysis of the impact of dilutions and chemical differences of mechlorethamine application in patients with CIM. In a recent review by Ramsay et al,[3] no distinction was made between allergic dermatitis and irritant dermatitis; however, there was a clear distinction between allergic contact dermatitis and irritant contact dermatitis in a previous study.[19] The histological findings in our study also showed the distinction between allergic dermatitis and irritant dermatitis, and spongiotic dermatitis was shown to be the most frequent histological pattern of CIM.

A mild cutaneous irritation is usually observed at the site of mechlorethamine application, especially in intertriginous sites and at lesion sites.[6] Severe irritation is usually observed in patients who received prior treatment with radiotherapy, or who have atopic skin or erythroderma.[19] In these cases, the concentration and/or the frequency of mechlorethamine application can be reduced temporarily until the disappearance of erythema and pruritus. Concurrent administration of local corticosteroids and emollients can reduce cutaneous irritation. In addition, short-term application of mechlorethamine probably could help reduce irritant dermatitis, but its effectiveness at preventing allergic dermatitis has yet to be demonstrated. This decreased effectiveness is due to mechlorethamine's rapid breakdown into its ionized form which cross-reacts in hypersensitivity reactions,[19,20,25] when dissolved in water. Vonderheid[19] observed that excessive irritation led to discontinuation of the treatment in only 10% of the patients. In the present study, 12 of the 23 patients resumed topical mechlorethamine therapy after resolution of CIM and 8 of the 12 did not show histological features of spongiotic dermatitis. Of the 8, biopsy specimens in 2 patients showed histological features of irritant dermatitis. The 8 patients were able to resume sustained application of mechlorethamine.

Accepted for publication June 29, 1999.

From the Department of Dermatology, Hôpital R. Debré, Reims and Hôpital Porte Madeleine, Orléans (Dr Estève); the Departments of Dermatology (Dr Bagot) and Pathology (Dr Wechsler), Hôpital H. Mondor, Créteil; the Departments of Dermatology (Dr Joly) and Pathology (Dr Thomine), Hôpital C. Nicolle, Rouen; the Department of Dermatology, Hôpital Hôtel Dieu, Clermont-Ferrand (Dr Souteyrand); Hôpital du Haut-Leveque, Pessac (Dr Beylot-Barry); Hôpital Trousseau, Tours (Dr Vaillant); Cente J. Perrin, Bordeaux (Dr Delaunay); Institut G. Roussy, Villejuif (Dr Avril); Hôpital Avicenne, Bobigny (Dr Laroche); Hôpital L. Pasteur, Colmar (Dr Grange), France.

The members of The French Study Group of Cutaneous Lymphomas included the authors of this article and Jacques Bosq, MD, Institut Gustave Roussy, Villejuif; Marie Helene Delfau-Larue, MD, Hôpital H. Mondor, Creteil; Béatrice Vergier, MD, Jean Pierre Merlio, MD, and Pierre Dubus, MD, Hôpital du Haut-Lévèque, Pessac; Christine Bodemer, MD, Sylvie Fraitag, MD, and Elizabeth MacIntyre, MD, Hôpital Necker, Paris; Sophie Dalac, MD, and Tony Petrella, MD, Hôpital du Bocage, Dijon; Frédéric Maître, MD, Hôpital Porte Madeleine, Orléans; Philippe Bernard, MD, PhD, Anne Durlach, MD, and Pascale Cornillet, MD, Hôpital R. Debré, Reims; Nathalie Franck, MD, and Agnes Carlotti, MD, Hôpital Tarnier, Paris; Marie-Claire Tortel, MD, and Anne Colson, MD, Hôpital Pasteur, Colmar; Philippe Courville, MD, and Bernard Lenormand, MD, Hôpital C. Nicolle, Rouen; Liliane Laroche, MD, PhD, and Marianne Asso-Bonnet, MD, Hôpital Avicenne, Bobigny; Anne de Muret, MD, Hôpital Trousseau, Tours; Michel

D'Incan, MD, and Pierre Dechelotte, MD, PhD, Hôpital Hôtel Dieu, Clermont-Ferrand; Brigitte Dréno, MD, PhD, and Elizabeth Cassagnau, MD, Hôpital Hôtel Dieu, Chu Nantes.

Reprints: Eric Estève, MD, Department of Dermatology, Hôpital Porte Madeleine, BP 2439-45032, Orléans Cedex 1, France.

REFERENCES

1. Ramsay DL, Parnes RE, Dubin N. Response of mycosis fungoides to topical chemotherapy with mechlorethamine. *Arch Dermatol*. 1984;120:1585-1590.
2. Ramsay DL, Halperin PS, Zeleniuch-Jacquotte A. Topical mechlorethamine therapy for early stage mycosis fungoides. *J Am Acad Dermatol*. 1988;19: 684-691.
3. Ramsay DL, Meller JA, Zackheim HS. Topical treatment of early cutaneous T-cell lymphoma. *Hematol Oncol Clin North Am*. 1995;9:1031-1056.
4. Kim YH, Jensen RA, Watanabe GL, Varghese A, Hoppe RT. Clinical stage IA (limited patch and plaque) mycosis fungoides: a long-term outcome analysis. *Arch Dermatol*. 1996;132:1309-1313.
5. Bunn PA Jr. Rational therapy for cutaneous T-cell lymphomas in the 1990s: fact or fancy? *Arch Dermatol*. 1995;131:603-605.
6. Vonderheid EC, Van Scott EJ, Johnson WC, Grekin DA, Asbell SO. Topical chemotherapy and immunotherapy of mycosis fungoides: intermediate-term results. *Arch Dermatol*. 1977;113:454-462.
7. Volden G, Molan L, Thomsen K. PUVA-induced suppression of contact sensitivity to mustine hydrochloride in mycosis fungoides. *BMJ*. 1978;876:865-866.
8. Leshaw S, Simon RS, Baer RL. Failure to induce tolerance to mechlorethamine hydrochloride. *Arch Dermatol*. 1977;113:1406-1408.
9. Monk BE, Vollum DI, du Vivier AW. Combination topical nitrogen mustard and photochemotherapy for mycosis fungoides. *Clin Exp Dermatol*. 1984;9:243-247.
10. Pariser DM, Childrers RC, Kechijian P, Halprin KM, Taylor JR. Intravenous desensitization to mechlorethamine in patients with psoriasis. *Arch Dermatol*. 1976; 112:1113-1114.
11. Nusbaum BP, Edwards EK, Horwitz SN, Frost P. Psoriasis therapy: the effect of UV radiation on sensitization to mechlorethamine. *Arch Dermatol*. 1983;119:117-121.
12. Halprin KM, Comeford M, Presser SE, Taylor JR. Ultraviolet light treatment delays contact sensitization to nitrogen mustard. *Br J Dermatol*. 1981;105: 71-76.
13. Waldorf DS, Haynes HA, Van Scott EJ. Cutaneous hypersentitivity and desensitization to mechlorethamine in patients with mycosis fungoides lymphoma. *Ann Intern Med*. 1967;67:283-290.
14. Avril MF. La caryolysine locale. *Ann Dermatol Venereol*. 1987;114:133-141.
15. Constantine VS, Fuks ZY, Farber EM. Mechlorethamine desensitization in therapy for mycosis fungoides: topical desensitization to mechlorethamine (nitrogen mustard) contact hypersensitivity. *Arch Dermatol*. 1975;111:484-488.
16. Vonderheid EC, Tan TT, Kantor AF, Shrager L, Micaily B, Van Scott EJ. Long-term efficacy, curative potential, and carcinogenicity of topical mechlorethamine chemotherapy in cutaneous T cell lymphoma. *J Am Acad Dermatol*. 1989; 20:416-428.
17. Adams RM, Fisher T. Diagnostic patch testing. In: Adams RM, ed. *Occupational Skin Diseases*. 2nd ed. Philadelphia, Pa: WB Saunders Co; 1990:223-253.
18. Price NM, Hoppe RT, Deneau DG. Ointment-based mechlorethamine treatment for mycosis fungoides. *Cancer*. 1983;52:2214-2219.
19. Vonderheid EC. Topical mechlorethamine chemotherapy: considerations on its use in mycosis fungoides. *Int J Dermatol*. 1984;23:180-186.
20. Price NM, Deneau DG, Hoppe RT. The treatment of mycosis fungoides with ointment-based mechlorethamine. *Arch Dermatol*. 1982;118:234-237.
21. Van Scott EJ, Kalmanson JD. Complete remissions of mycosis fungoides lymphoma induced by topical nitrogen mustard (HN_2): control of delayed hypersensitivity to HN_2 by desensitization and by induction of specific immunologic tolerance. *Cancer*. 1973;32:18-30.
22. Price NM. Topical mechlorethamine: cutaneous changes in patients with mycosis fungoides after its administration. *Arch Dermatol*. 1977;113:1387-1389.
23. Daughters D, Zackheim H, Maibach H. Urticaria and anaphylactoid reactions after topical applications of mechlorethamine. *Arch Dermatol*. 1973;107:429-430.
24. Newman JM, Rindler JM, Bergfeld WF, Brydon JK. Stevens-Johnson syndrome associated with topical nitrogen mustard therapy. *J Am Acad Dermatol*. 1997; 36:112-114.
25. Van Scott EJ, Yu RJ. Antimitotic, antigenic, and structural relationships of nitrogen mustard and its homologues. *J Invest Dermatol*. 1974;62:378-383.
26. Cordonnier J. Lettre de la direction de la pharmacie et du médicament à propos des préparations magistrales de pommade à base de méchloréthamine. *Ann Dermatol Venereol*. 1985;112:293.