Topical Bleomycin-dimethylsulfoxide in AIDS Kaposi’s Sarcoma

Sir,

The treatment of Kaposi’s sarcoma in the acquired immunodeficiency syndrome (AIDS) requires systemic chemotherapy or interferon for disseminated disease. In patients with few lesions, such a treatment is difficult to consider. Many alternatives have been proposed, including radiotherapy, laser, intralesional vincristine or bleomycin and, recently, liquid nitrogen and sclerotherapy (1, 2). Cosmetics may also add to the treatment of the psychological aspect of the disease.

We tried a topical treatment with bleomycin (BLM) diluted in dimethylsulfoxide (DMSO), firstly to reduce systemic toxicity, secondly to have the maximal concentration of the drug at the tumor site and thirdly to have the potential differentiating effect of DMSO.

We used the same dosage of BLM as in systemic chemotherapy, i.e. a total of 5 mg per day during 5 days, repeated every 2 weeks until total disappearance of the lesions. BLM was diluted in DMSO and applied on patch test devices (Leukotest, BDF Medical, Le Plessis Robinson, France), which were applied to the skin lesions for 12 h and then removed. Regular blood examination was performed during the treatment.

The determination of bleomycin metabolites A2 and B2 in the patient’s sera was performed by using a liquid chromatographic method with UV spectrophotometry according to the technique of Shi et al. (3). DMSO and dimethylsulfoxide (DMSO2) in serum were quantified by gas chromatography employing a flame ionization detector according to the technique of Mehta et al. (4). Each dosage was performed before and 5, 15, 30, 45 min, and 1, 2, 3, 6, 9, 12, 24 h after the application of the BLM-DMSO mixture. Using these chromatographic methods, we were able to detect serum concentrations of BLM A2, BLM B2, DMSO and DMSO2, respectively equivalent to 0.1 mg l-1, 0.2 mg l-1, 25 mg l-1 and 25 mg l-1.

CASE REPORTS

Case 1

A 30-year-old man, serologically positive for the human immunodeficiency virus in 1989, was included in the Concorde protocol (InsERM, France). He first developed biopsy-proven Kaposi’s sarcoma in December 1989 and presented 3 maculopapular lesions of the thighs after 2 months. He gave his informed consent to the treatment. Five mg of BLM diluted in 0.5 ml DMSO were applied per day during 3 days. After a total of 6 courses, we observed the clinical disappearance of Kaposi lesions (lightly pigmented macules). Histopathology showed less important lesions. A clinical recurrence of the lesions appeared in September 1990. The topical treatment was then reintroduced, with good results. However, he developed a pulmonary infection due to atypical mycobacteria and died in May 1991.

Case 2

A 34-year-old man had been HIV positive since 1987. He presented with 5 Kaposi’s sarcoma papular lesions in December 1990, and he gave his informed consent to the treatment. BLM was diluted in 1 ml of DMSO and applied in February 1991 as described in Case 1. He received a total of 5 courses with a disappearance of the violaceous hue and of the infiltration of the lesions, but a pigmentation of the test area was observed. A widespread eruption of Kaposi lesions appeared in July 1991, and BLM was given by the intramuscular route with stabilization of the lesions. The lesions primarily treated by topical BLM were again papular in January 1992. The subsequent worsening of the Kaposi’s sarcoma led to the patient’s death in May 1992.

BLM A2 and BLM B2, DMSO and DMSO2 serum concentrations measured in both patients were never present above the lower limit of quantification.

DISCUSSION

In many patients, Kaposi’s sarcoma begins with few lesions and its treatment is actually not standardized. Many therapies have been proposed. Our aim was to use topically a chemotherapeutic agent which is known to be active in a systemic form. We tried BLM in a vehicle also known for enhancing skin penetration. DMSO is used in treating extravasation of anthracyclin and vinca alkaloids alone or with alpha tocopherol with good therapeutic effects and without local and systemic toxicity (5–7). The quantity of DMSO was different in our two patients because we needed to treat all the lesions; 0.5 ml was used to treat 3 lesions in the first patient and the double quantity to treat 5 lesions in the second patient. Systemic toxicity was not observed in our two patients, as shown by regular blood examination, and we did not find BLM A2, BLM B2, DMSO and its metabolite in their different serum samples.

We observed a good therapeutic effect which lasted some months. The recurrence of the disease could be due to an incomplete effect, as shown by histopathology in our first patient, or to the rapid evolution of the disease, as in our second patient. A problem was the pigmentation we observed with topical BLM. It is a well-known side-effect with systematically used BLM, of unknown mechanism. The role of BLM is evident in our case by the pigmentation of all the device area, and it cannot be regarded as pigmented sequelae of treated Kaposi lesioins.

This method is actually of limited value because of its temporary effect, but its efficacy and feasibility are important to consider. It may represent a new way of treating Kaposi’s sarcoma, but many immunosuppressive drugs may have pigmenting side-effects.

REFERENCES


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Mycosis Fungoides and Allogenic Bone Marrow Transplantation

Sir,

Mycosis fungoides belongs to the group of cutaneous T-cell lymphomas (CTCL) where there is a proliferation of T-lymphocytes which, in the majority of cases, exhibit the phenotypic and functional properties of T-helper cells. The prognosis depends on the degree of lymph node and organ involvement (1), the stage according to the international tumor-node-metastasis (TNM) classification (2) and the serum lactate dehydrogenase level (LDH) (3). We report the case of a young patient with and advanced TNM stage IVa CTCL with a poor prognosis, who responded inadequately to combination chemotherapy and whom we decided to treat with an allogeneic bone marrow transplantation. We present the results from a follow-up period of more than 5 years and we discuss the place of autologous or allogenic bone marrow transplantation in treating poor prognosis CTCL.

CASE REPORT

In 1979, a 21-year-old woman presented with lichenified eczema on the trunk, forearms and lower limbs. The eczema varied in severity, and the diagnosis was confirmed histologically. She had previously suffered from asthma. A diagnosis of atopic dermatitis was made and several courses of local treatment were tried, including local corticosteroids, anti-histamines and PUVA therapy; however, the response was for the most part short-lived.

In 1987, when the patient was 29 years old, she observed an exacerbation of the initial lesions with an infiltration of the previously affected areas and the appearance of tumoral lesions. Clinical examination revealed multiple highly infiltrated patches with a tumoral appearance on the trunk, the upper and lower limbs and the scalp, some of which were ulcerated, a tumor of 4.5 cm x 2.5 cm x 0.7 cm on the back and multiple erythematous squamous papules, which were only slightly infiltrated and were spread all over the skin. There was periumural alopecia of the scalp. The mucous membranes and nails were normal. Superficial lichenoid dermatitis without hepatosplenomegally was also present. Her general health was unaffected and she was febrile.

Laboratory investigations revealed a normal full blood count with a normal total white blood cell count (9310/mm³), a total lymphocyte count 1350/mm³ consisting of 45% T-helper cells (CD4 total: 580/mm³) and 15% T-suppressor cells (CD8 total: 576/mm³) with a T4/T8 ratio of 2.2, no circulating Sézary cells being observed. An in vivo study of cellular immunity using a multiple prim-test for trichophyton, candida, tetanus, diphtheria, streptococcus and tuberculosis proteins was completely negative. HIV-1 and HIV serology was negative. Total IgG was increased to 367 kU/L (N < 150 kU/L). Serum LDH was increased to 540 U/L (N < 320 U/L).

Histological examination of a skin nodule revealed a dense, monomorphic proliferation consisting of atypical mononucleated cells with hyperconvoluted cerebriform nuclei and multiple mitoses, which infiltrated the dermis, epidermal exocytosis being present in places, giving the appearance of Pautrier microabscesses. Biopsy of an axillary lymph node showed infiltration by numerous T-cells with cerebriform nuclei in the paracortical and medullary areas. The capsule was not infiltrated.

The immunophenotype of the skin and lymph nodes was the same, revealing the existence of a proliferation predominantly of mature T-helper cells with the phenotype: CD3 + CD4 + CD5 + CD7 +, HLA DR +, CD21 +, with a normal T4/T8 ratio of 1.66. There were no chromosomal abnormalities of the lymph node karyotype. Computerized tomography of the chest and abdominal was normal. According to the international TNM classification for CTCL (2), it was a stage IVa tumor.

A systemic combination chemotherapy regimen was commenced on a monthly basis, consisting of 5.6 mg bleomycin, 60 mg adriamycin, 840 mg cyclophosphamide and 1.4 mg vincristine all on day 1, 8.5 mg dexamethasone from day 1 to 5 and 2.1 g methylxosone on day 15 (M-Bacod). Eight cycles were given, resulting in a partial remission and a moderate decrease in the cutaneous tumors and lymphadenopathy.

We then decided to proceed with an allogeneic bone marrow transplantation in view of the patient's young age, the poor response to combination chemotherapy, the existence of an HLA histocompatible donor, her brother, and the results already obtained by treating refractory lymphoma with allogeneic bone marrow transplantation.

Preparation of the bone marrow prior to transplantation was begun with two doses of 60 mg/kg cyclophosphamide and total body irradiation (TBI), with interposition of a bolus of electrons, in order to deliver the maximum dose of 9.9 Gy to the skin, the reference dose for total irradiation being 11 Gy. The bone marrow transplantation was performed in October 1987, the patient receiving 4 x 10⁸ cells/kg. The prevention of graft-vs-host disease (GVHD) included methotrexate (days 1, 3 and 6); cyclosporine (days 0 to 100); prednisone (days 30 to 80) and a daily infusion of anti-interleukin 2 receptor monoclonal antibodies (days 15 to 30). Complications from the transplantation included an episode of staphylococcus aureus septicemia. No signs of GVHD were observed.

In December 1987, on day 70, a complete remission of the old lesions was observed, but there was a relapse with non-infiltrated, erythematous, squamous lesions which were 5 cm in diameter, localized in the right and left axilla, the right axilla and the right elbow fold. Clinical examination did not reveal any organ or lymph node disease. This mild early local relapse was treated with local electron therapy at a dose of 20 Gy and total body electron beam therapy dosed at 20 Gy.