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 allogenic 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, antihistamines 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 × 2.5 cm × 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 peritumoral alopecia of the scalp. The mucous membranes and nails were normal. Superficial lymphadenopathy without hepatosplenomegaly was also present. Her general health was unaffected and she was afebrile.

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 43% T-helper cells (CD4 total: 580/mm³) and 19% T-suppressor cells (CD8 total: 256/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 prick-test for trichophytum, candida, tetanus, diphtheria, streptococcus and tuberculin proteins was com-

pletely negative. HTLV1 and HIV serology was negative. Total IgE 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 chemotheraphy 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 methotrexate 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 allogenic 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 allogenic 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 × 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 scapular, 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 Gys and total body electron beam therapy dosed at 20 Gys. The

medullary and blood karyotypes showed complete chimaerism with exclusively masculine mitoses.

By July 1991, two morphea lesions were noted in the supero-lateral quadrant and sub-mammary region of the right breast, suggesting the presence of chronic GVHD. Two and a half years after the bone marrow transplantation, anti-polyomyelitis and tetanus vaccinations (Pasteur®) were attempted but no reaction was produced. No seroconversion of the specific antibodies was found, showing the persistence of an immuno-deficient state as part of chronic GVHD. However, owing to the mildness of the symptoms, no specific treatment was necessary.

In January 1992, nearly 4 years after the transplantation, a small papular, pruriginous lesion localized in the right axilla had been noted by the patient during the previous 2 months. The lesion rapidly disappeared with two courses of clobetasol propionate (Dermovate®).

One month after the reappearance of the lesion in the right axilla, a skin biopsy was performed which confirmed that there had been a relapse of the lymphoma. There was no superficial lymphadenopathy. Computerized tomography of the chest and abdominal was normal, as were myelogram and osteo-medullar biopsy. The karyotype only showed donor cell mitoses.

Local electron irradiation dosed at 50 Gys over five sessions was followed by 3×10^6 IU of alfa-2a interferon subcutaneously three times a week for a year. Up to November 1993, after another follow-up period of 22 months, and 6 years after the transplantation, no recurrence was observed.

DISCUSSION

Various factors led us to decide on allogenic bone marrow transplantation for our patient: the poor prognosis of late-stage CTCL, her young age, the partial remission obtained after combination chemotherapy similar to M-Bacod, which is used for high-grade malignancy lymphomas, and finally the fact that her brother had the same genotype. It is now generally agreed that autologous bone marrow transplantation is the first-line treatment to maintain the results obtained in the treatment of lymphomas with an initially poor prognosis (tumoral extension, stage with a poor prognosis, serum LDH value), or as second-line treatment following a relapse. Randomized studies have produced a cure rate of 35% in patients still sensitive to chemotherapy (4). However, in refractory patients, the effectiveness of autologous bone marrow transplantation has not yet been demonstrated (4). Allogenic bone transplantation is indicated in those cases of lymphoma with a poor prognosis. By analogy with non-Hodgkin's lymphoma (5–9), it is feasible that bone marrow transplantation may help CTCL (10). However, controlled randomized trials are essential to investigate if there is any true benefit to be gained in using this treatment in place of conventional chemotherapy regimes. Preparation of the bone marrow prior to transplantation must in all cases be both directed against the lymphoma and myeloablative and, for allogenic bone marrow transplants, it should probably also be immunosuppressive. Marrow preparation is the same for both types of bone marrow transplant, but in view of the extrahematological toxicity of high-dose chemo-radiotherapy, the doses cannot be increased further (6 to 8 times the conventional doses).

Before embarking on bone marrow transplantation, one should take two important points into account: the choice of the type of bone marrow transplantation and the mortality risk involved. Autologous bone marrow transplantation eliminates the risk of GVHD, offers the chance of a transplant in the absence of a histocompatible donor (only available for 20% of patients) and can be performed in patients up to 60 years old. The effectiveness of autologous transplantation is limited by the risk of re-injection of residual malignancy cells, but above all by the absence of a graft-versus lymphoma (GVL) effect, which may occur following allogenic bone marrow transplantation. The toxic mortality of 20% following allogenic transplantation, compared with less than 5% after autologous transplantation (these data are from our personal experience), is in fact caused by GVHD produced by the donor T-lymphocytes. However, if GVHD is controlled, these patients have significantly fewer relapses compared to those treated by autologous, syngenic or T-lymphocyte depletion transplantations, which do not induce a GVL effect.

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Marie-Christine Koeppel[1], Anne-Marie Stoppa[2], Michel Resbeut[3], Didier Blaise[2], Michel Coignet[1], Lucienne Coulier[1], Dominique Maraninchi[2] and Jacqueline Sayag[1], [1]Department of Dermatology, Timone Hospital and Departments of [2]Haematology and [3]Radiotherapy, Institute of Paoli Calmettes, Marseille, France.