

CASE REPORT

Autologous Hematopoietic Stem Cell Transplantation Followed by Oral Bexarotene in a Patient With Advanced Mycosis Fungoides

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Abstract. We describe the case of a 17-year-old patient with rapidly progressing and aggressive mycosis fungoides, with multiple cutaneous tumors and large cell transformation. She was initially treated with 3 cycles of high-dose chemotherapy with mega-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) without response, leading to the decision to undertake autologous hematopoietic stem cell transplantation. Partial remission of the disease was achieved with this treatment and subsequent introduction of oral bexarotene led to complete remission, which has been maintained for more than 3 years with good tolerance of oral therapy. We discuss the advantages and disadvantages of autologous hematopoietic stem cell transplantation and the use of oral bexarotene.

Key words: autologous hematopoietic stem cell transplant, bexarotene, cutaneous T-cell lymphoma, mycosis fungoides.

TRASPLANTE AUTÓLOGO DE PROGENITORES HEMATOPOYÉTICOS SEGUIDO DE BEXAROTENO ORAL EN PACIENTE CON MICOSIS FUNGOIDE AVANZADA

Resumen. Exponemos el caso de una paciente de 17 años que presentó una micosis fungoide de evolución rápida y agresiva, con múltiples tumores cutáneos y transformación fenotípica celular a linfoma de células grandes. Fue tratada inicialmente con 3 ciclos de quimioterapia en dosis altas (MEGA-CHOP) sin respuesta, por lo que se decidió realizar un trasplante autólogo de progenitores hematopoyéticos. Este tratamiento consiguió una remisión parcial de la enfermedad, y con la posterior introducción del bexaroteno oral se logró la remisión completa, que se ha mantenido durante más de 3 años con muy buena tolerancia al bexaroteno oral.

Analizamos las ventajas y desventajas de la utilización del trasplante autólogo de progenitores hematopoyéticos y del uso de bexaroteno oral.

Palabras clave: trasplante autólogo de precursores hematopoyéticos, bexaroteno, linfoma cutáneo de células T, micosis fungoide.

Introduction

Mycosis fungoides represents 50% of all primary cutaneous lymphomas and is the most common type of cutaneous T-cell lymphoma (CTCL). The incidence of the disease is 0.4 cases per 100 000 inhabitants per year.¹ It is most common in adults in their 60s and 70s, although it may

occasionally appear in adolescents and even in children. In the case of young patients, close monitoring is required, as the disease tends to progress more rapidly and aggressively in such patients, developing into large cell lymphoma. This transformation is said to have occurred when a tumor infiltrate in which more than 25% of the cells are 4 times or more the size of healthy lymphocytes is found.

The incidence of such transformations ranges from 8% to 39%, and is associated with a poor prognosis.²

Case Description

The patient, now 26 years of age, developed extensive clinically and histologically nonspecific patches on her thighs in 1996. Over a 3-year period, during which she

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was lost to follow-up, similar lesions appeared progressively on her trunk, upper extremities, and neck. The lesions became raised during the last year. In 1999 she developed several cutaneous tumors on plaque-like lesions and generalized enlarged lymph nodes within a period of a month. The pathology report on one of the tumors showed a diffuse dermic lymphoid infiltrate with epidermotropism, focal ulceration, parakeratosis, loss or atrophy of skin appendages, presence of Pautrier microabscesses, and abundant eosinophils. The infiltrate was very dense and was composed of dual phenotype lymphoid cells: small cells with hyperchromic nuclei and a markedly indented contour and larger lymphoid cells with a blastic appearance. According to immunohistochemistry, most of the lymphocytes were T cells positive for CD3 and CD4 with an accompanying population of B cells positive for CD20 and T cells positive for CD8, as well as dendritic cells. Computed tomography showed greatly enlarged bilateral axillary lymph nodes and less enlarged lymph nodes in the groin area. Histology of an axillary lymph node confirmed lymphoma infiltration. However, bone marrow biopsy was normal (TNMB stage IV-A).

The histologic study of a new tumor performed 4 months later showed mycosis fungoides type CTCL in transformation to large T-cell lymphoma, and loss of mature peripheral phenotype (CD3⁺, CD4⁻, CD20⁻ CD30⁺ in isolated clusters of cells). The large cells accounted for 80% of the infiltrate, and 60% of them expressed Ki-67. The remaining infiltrate was composed of small CD4⁺ and CD8⁻ cells (Figures 1, 2, and 3). With polymerase chain reaction methods, T-cell receptor gene rearrangement was positive for the γ -1 chain in both blood and skin. The changes detected in the immunophenotypic analysis of peripheral blood did not confirm diagnosis of CTCL.

In view of the rapid progression of the disease, in April 1999 the patient began high-dose chemotherapy with 3 cycles of mega-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) administered together with granulocyte colony stimulating factor (G-CSF), with poor response. Due to the characteristics of the patient and the aggressiveness of the lymphoma, we decided to perform autologous hematopoietic stem cell transplantation (HSCT), which was carried out in November 1999. The patient had previously received a total of 4 cycles of ESHAP (etoposide, high-dose cytarabine, cisplatin, and methylprednisolone) as salvage chemotherapy. Autologous stem cells were collected following mobilization with cyclophosphamide and G-CSF. The patient received the BUCY 2 (busulphan and cyclophosphamide) conditioning regimen for HSCT and mesna and phenytoin to prevent the appearance of hemorrhagic cystitis and epileptic seizures, respectively. Although the patient tolerated treatment well and response was good, the lesions reappeared as plaques in January 2000, but with no clinical or imaging evidence

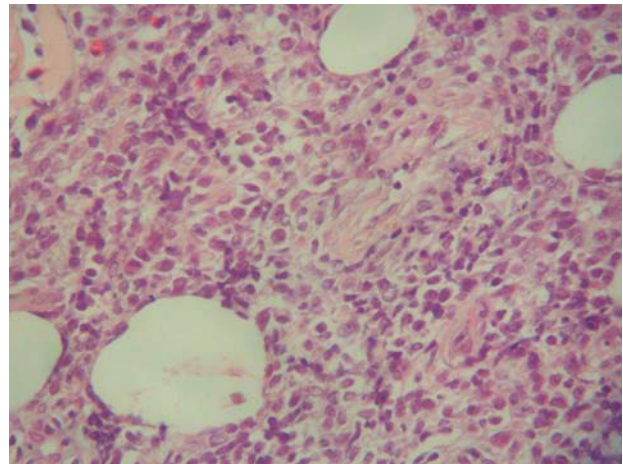


Figure 1. Histologic image showing a diffuse lymphoid infiltrate, 80% of which is composed of large cells (hematoxylin-eosin, original magnification $\times 200$).

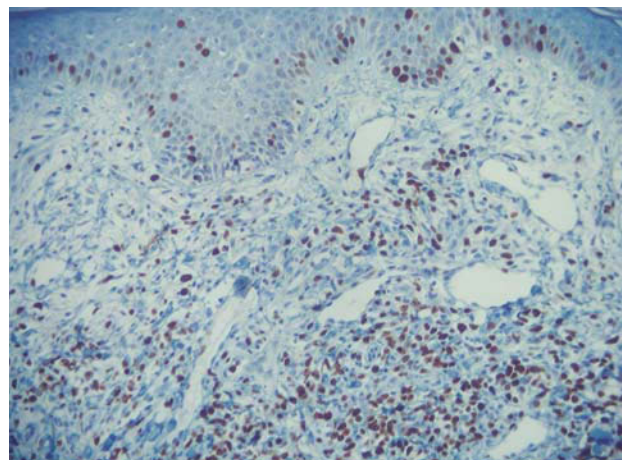


Figure 2. In this infiltrate nuclear positive staining for Ki-67 was observed in 60% of the cells. This shows its high proliferative index (Ki-67, original magnification $\times 200$).

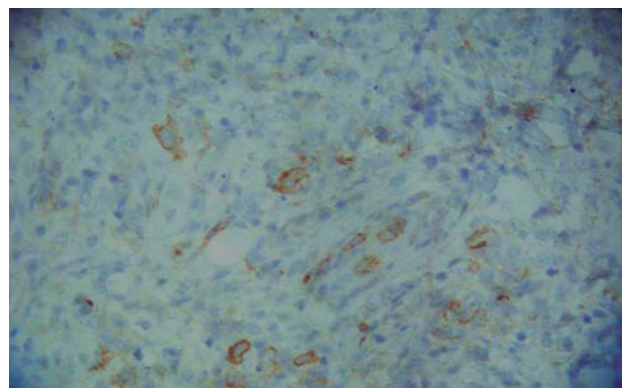


Figure 3. Only isolated clusters of large CD30⁺ cells can be seen (CD30, original magnification $\times 200$).

of associated enlarged lymph nodes (stage I-B) (Figure 4). The lesions were treated with nitrogen mustard and topical corticosteroids, followed by psoralen UV-A (PUVA) and interferon (IFN) α -2b up to a maximum of 4.5 million

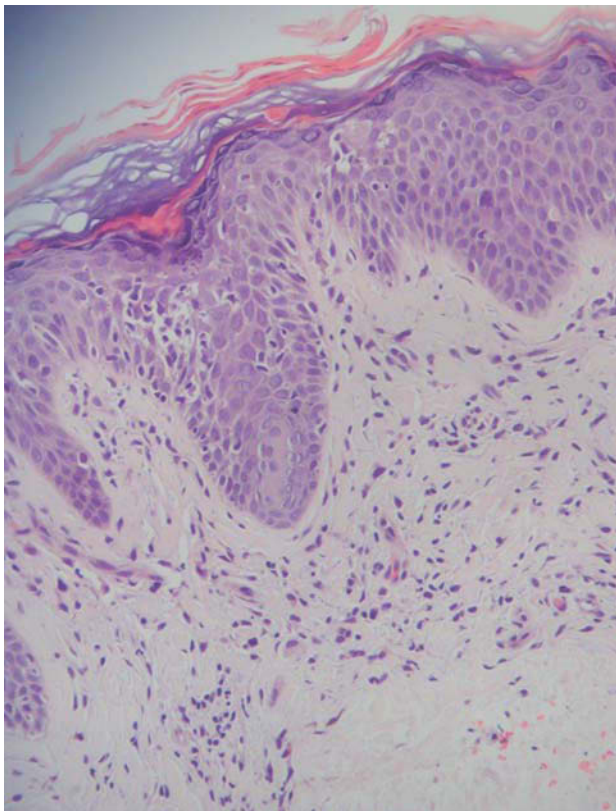


Figure 4. Histologic image of one of the lesions that reappeared in January 2000, showing plaque-like mycosis fungoides with epidermotropism and minor lymphocytic infiltration of the superficial dermis (hematoxylin-eosin, original magnification $\times 100$).

units 3 times per week. Local radiation therapy was required on several occasions, due to the rapid growth of the tumors, predominantly in the cervicocephalic region (in 2001) (stage II-B) (Figure 5).

In view of the evident cutaneous progression of the disease, we initiated treatment with oral bexarotene at the beginning of 2003. It was well tolerated, and the clinical response was spectacular, as the patient presented only residual hypopigmented lesions, with no infiltration, and these have remained stable. We therefore consider the patient to be in complete remission after 42 months of follow up (Figure 6).

Discussion

HSCT after the application of myeloablative chemotherapy or radiation therapy has been shown to be curative in various myelolymphoproliferative disorders. However, little has been published in relation to its use in treating CTCL. It is especially indicated in patients under 60 years old with no comorbidity or severe organic dysfunction (particularly cardiac, kidney, or lung dysfunctions) and advanced or rapidly progressing neoplastic disease that has been refractory to at least 1 systemic therapy.

Autologous HSCT consists of myeloablative chemotherapy followed by the infusion of hematopoietic stem cells previously obtained from the patients themselves. It has the advantage of being safe, with low rates of morbidity and mortality, and of being relatively accessible, as it can be performed at advanced ages and does not require histocompatible donors. In most cases, complete but short-lasting remission is obtained. Recurrence is believed to be due both to the reinfusion of tumor cells together with the graft from the patients themselves and to the problems



Figure 5. Clinical image of the neck tumor that grew rapidly over the course of a month.



Figure 6. Clinical image showing the patient's present state, with only residual hypopigmented lesions on the thighs.

experienced by a deteriorated immune system combating residual disease. Another possibility to be considered is the failure of chemotherapy to eradicate the disease, with these residual chemoresistant clones ultimately being responsible for recurrence.

The high rates of recurrence of CTCL after chemotherapy and autologous HSCT are comparable to those found in other low grade lymphomas, in which this type of therapy has been used for longer.

Allogenic HSCT can also induce complete remissions in low grade lymphomas. The recurrence rate is lower than with autologous transplants (18% compared to 46%) and disease-free survival is increased by months or even years. Although this treatment has so far only been used in a few cases of CTCL, similar results have been obtained. The use of allogenic stem cells not only eliminates contamination of the graft by malignant cells, but also has an antitumoral effect (known as the graft-vs-lymphoma effect) that is usually directly proportional to the graft-vs-host reaction. However, unlike autologous HSCT, the mortality rate from the procedure is high (approximately 20%), especially in view of the fact that it is performed in heavily pretreated patients with advanced disease. Progress has been made in the treatment of graft-vs-host reactions thanks to new immunosuppressive therapies such as the so-called minitransplants, which consist of using less intensive conditioning regimens that decrease toxic mortality and aim to obtain a greater graft-vs-lymphoma effect. Such transplants can thus be performed in a wider range of patients, some of them of advanced age. Unfortunately, these therapies are still in the development stage.^{3,4}

Bexarotene was approved by the American Food and Drug Administration at the end of 1999 for the treatment of CTCL refractory to at least 1 prior systemic therapy. The drug, a rexinoid, is a selective retinoid X nuclear receptor agonist. These receptors modulate the expression of genes that act to inhibit the proliferation of tumor cells and the induction of cell differentiation and apoptosis, although their exact mechanism of action is unknown. The recommended daily dose is 300 mg/m² per day and the most common adverse effects are hyperglyceridemia and central hypothyroidism. Both of these are reversible and dose-dependent.⁵

Our patient was a young woman with initially aggressive mycosis fungoides. In the course of her disease, a phenotypic transformation of cells to a large cell lymphoma occurred with poor response to chemotherapy. Autologous HSCT managed to resolve the lymphadenopathy and systemic disease, limiting the disease to the skin (probably by controlling the phenotypic variation of the large cell lymphoma). The immunomodulating effect of autologous HSCT not only managed to slow the progression of the disease at a critical moment and attenuate its later aggressiveness, but also to reduce the tumor mass from

which it arose. It promoted a good subsequent response to oral bexarotene, making it possible for the patient to currently be in complete remission after more than 3 years. The hypothesis that bexarotene therapy could be effective is supported by several studies that have reported success with combinations of bexarotene and PUVA,⁶⁻⁸ interferon- α ,⁹ photopheresis,¹⁰ and denileukin diftitox.^{11,12} A combination of bexarotene and denileukin diftitox has been shown even in in vitro studies to have a synergic effect. In the case we report, we combined autologous HSCT with subsequent bexarotene therapy. The consecutive use of these 2 therapies has not been previously described, and we think it is an option worth considering in the treatment of CTCL, especially those with aggressive progression to large cell lymphoma.

Conflicts of Interest

The authors declare no conflicts of interest.

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