OBSERVATION

Long-term Remission After Allogeneic Hematopoietic Stem Cell Transplantation for Refractory Cutaneous T-Cell Lymphoma

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Background: Allogeneic hematopoietic stem cell transplantation has proved to be an effective therapeutic option in various hematologic neoplastic disorders. Because patients with advanced cutaneous T-cell lymphoma have a poor prognosis, with minimal possibilities of sustained remission, we studied the therapeutic potential of hematopoietic stem cell transplantation.

Observations: Three young patients with refractory tumor stage mycosis fungoides underwent allogeneic HLA-matched sibling transplantation with combined marrow and CD34-enriched peripheral blood stem cell transplantation after cytoreductive chemotherapy and total-body irradiation. Complete and sustained clinical and histologic remission was achieved in 2 patients, and both remain disease free 4½ years and 15 months later. One patient was in complete remission for 9 months, followed by limited cutaneous recurrence. Mild graft-vs-host disease and graft-vs-tumor effect have contained the recurring disease as a low-grade process.

Conclusions: Allogeneic hematopoietic stem cell transplantation has the potential for sustained remission and the possibility of cure for young patients with advanced and recalcitrant cutaneous T-cell lymphoma. Even in the absence of complete remission, an allogeneic graft-vs-tumor effect may provide an immune mechanism to control the malignant T-cell process and alter the natural history of disease.

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CUTANEOUS T-CELL lymphoma (CTCL) is a malignant proliferation of T lymphocytes with homing features to the skin. In general, mycosis fungoides (MF) is an indolent process with slow progression from patches and plaques to tumors, although some patients experience a more aggressive course.[1-3] In the early stages, the malignant lymphocytes are mostly confined to the upper dermis, with prominent extension into the epidermis (epidermotropism). However, with time, CTCL cells may grow in the dermis, resulting in dermal tumors and eventually nodal and systemic involvement.[4] The most common immunophenotype expressed in CTCL is the $CD4^+$ $CD45RO^+$ memory-helper phenotype, with absence of CD7 expression.[5] Although the prognosis is good for the early stages, advanced CTCL tends to become refractory to treatment and has a poor prognosis. Sézary syndrome is the leukemic variant characterized by circulating clonal T lymphocytes with cerebriform nuclei and generalized erythroderma.

Although there are multiple successful treatment modalities for the early stages, advanced CTCL tends to respond poorly to therapy. Interferon alfa, extracorporeal photopheresis, single-agent and multiagent chemotherapy, radiation therapy, retinoids, and recombinant fusion proteins can provide significant and sustained palliation, but, in general, the period of remission tends to be short. There is no current therapy that can reliably provide long-term remission or cure for patients with advanced stage MF.[3]

Allogeneic and autologous hematopoietic stem cell transplantation (HSCT) is a well-established treatment option for various hematologic diseases and lymphoproliferative disorders. However, the type of graft significantly affects the rate of relapse. In patients with previously treated low-grade lymphoma, the allogeneic relapse rate was 18%, which represents a significant ($P = .02$) improvement compared with the relapse rate

of 46% for those with autologous grafts. This higher effectiveness of allogeneic transplants is most likely due to an immunologic graft-vs-lymphoma (GVL) effect.[6]

To our knowledge, we report the first series of successful allogeneic HSCT therapy in advanced CTCL. Reinduction of clinical and histologic remission after withdrawal of immunosuppressive medication provides evidence of a GVL-mediated remission in CTCL.

PATIENTS AND METHODS

PATIENT SELECTION

Patients with histologically confirmed MF who did not respond to psoralen–UV-A (PUVA) irradiation and at least 1 systemic therapy were candidates if an HLA-matched potential donor sibling existed. If criteria for the primary bone marrow transplantation protocol were fulfilled, including being younger than 55 years, Eastern Cooperative Oncology Group performance status of 0 or 1, and no major end organ dysfunction, candidates were offered an adjunct protocol to augment donor bone marrow with CD34-enriched peripheral blood stem cells. The secondary protocol for CD34-enriched peripheral blood stem cells is approved by the US Food and Drug Administration under investigational device exception number BB-IDE 6991.

SUPPORTIVE CARE

Patients were treated on a HEPA (high-efficiency particle arresting)–filtered unit to prevent infections. A low-microbial diet and treatment with fluconazole (400 mg/d, oral or intravenous), valacyclovir hydrochloride (500 mg 3 times daily, oral or intravenous), and ursodiol (300 mg 3 times daily, by mouth) were started on hospital admission and were discontinued when the absolute neutrophil count (ANC) rebounded to 500 cells/µL. Oral ciprofloxacin (750 mg twice daily, oral) was started on hospital admission, and switched to intravenous piperacillin sodium and tazobactam when the ANC declined below 500 cells/µL. During neutropenia, patients were confined to their rooms. Hand washing and glove use were required for all personnel entering a patient's room. Subcutaneous granulocyte colony-stimulating factor therapy (5 µg/kg) was started the day of hematopoietic stem cell infusion and continued until the ANC was greater than 1000/µL for 3 consecutive days.

STEM CELL COLLECTION

Donor marrow was harvested with the patient under general anesthesia. A mononuclear product was obtained using the Ficoll gradient technique and were cryopreserved in the vapor phase of liquid nitrogen. The following day, 10 µg/kg per day of granulocyte colony-stimulating factor (Amgen, Inc, Thousand Oaks, Calif) was given subcutaneously. A 10- to 15-L leukapheresis was performed on day 5 of granulocyte colony-stimulating factor therapy. If a minimum of 2.0×10^6 CD34 cells/kg was not available after enrichment, a second leukapheresis was performed on day 6.

CD34 ENRICHMENT

To diminish the risk of increasing graft-vs-host disease (GVHD), the peripheral blood stem cell harvest was lymphocyte depleted by $CD34^+$ selection using an immunoabsorption column (Ceprate; CellPro, Inc, Bothell, Wash). The enriched stem cell fraction was cryopreserved in the vapor phase of liquid nitrogen.

STEM CELL INFUSION

After completing the conditioning regimen with chemotherapy or chemoradiotherapy, the donor's hematopoietic stem cells are infused intravenously. By definition, the day of stem cell infusion is day 0. Engraftment is defined as an ANC greater than 500 cells/µL and a platelet count greater than 20×10^3/µL without transfusions.

GVHD PROPHYLAXIS

To prevent GVHD, patients received prophylaxis with cyclosporine, corticosteroids, and, in some cases, mycophenolate mofetil. Cyclosporine administration was started on day –1 at 5 mg/kg per day infused intravenously across 24 hours. Cyclosporine was switched to oral twice-daily dosing when the ANC was greater than 500 cells/µL. Cyclosporine administration is slowly tapered and discontinued, usually within 6 months of transplantation. Corticosteroid therapy was started on day 7 as either an intravenous methylprednisolone or an equivalent oral prednisone dose of 0.5 mg/kg per day. Corticosteroid dosages were increased to 1.0 mg/kg per day on day 15 and then tapered weekly until discontinuation on day 56.

REPORT OF CASES

CASE 1

A 36-year-old white man presented with a 5-year history of pruritic patches and plaques. Hyperpigmented plaques were present on 70% to 80% of the body surface area (T2), with thick hyperkeratotic palms and soles. The skin biopsy specimen was diagnostic for MF, and the patient was diagnosed as having MF stage IB. After 3 years of therapy with PUVA, interferon alfa, PUVA with interferon alfa, and spot radiation, the patient developed tumor lesions (T3). Sézary cells, lymphadenopathy, and hepatosplenomegaly were not detected at any time. After conditioning with cyclophosphamide (120 mg/kg) with mesna, total-body irradiation (1200 rad [12 Gy]), and allogeneic HLA-matched sibling transplantation, the posttransplantation course was complicated by mild and transient acute GVHD of the gastrointestinal tract (grade 3) and asymptomatic cytomegaloviremia that resolved with ganciclovir therapy. Cyclosporine use was discontinued 6 months after transplantation. Skin biopsy samples of residual hyperpigmented patches showed postinflammatory hyperpigmentation and no evidence of MF. The patient has been in complete remission for more than 4½ years without treatment or any signs of GVHD.

CASE 2

A 39-year-old African American woman presented with a 5-year history of a pruritic cutaneous eruption. Widespread reddish brown indurated patches and thick plaques were present on approximately 10% (T2) of the body, most notably on the face and trunk. The skin biopsy specimen showed MF large cell type with a $CD4^+$ $CD7^-$ immunophenotype. A T-cell clone was not detected by gamma T-cell receptor polymerase chain reaction (PCR). Her condition progressively worsened despite partial and temporary improvements with various treatment modalities, includ-

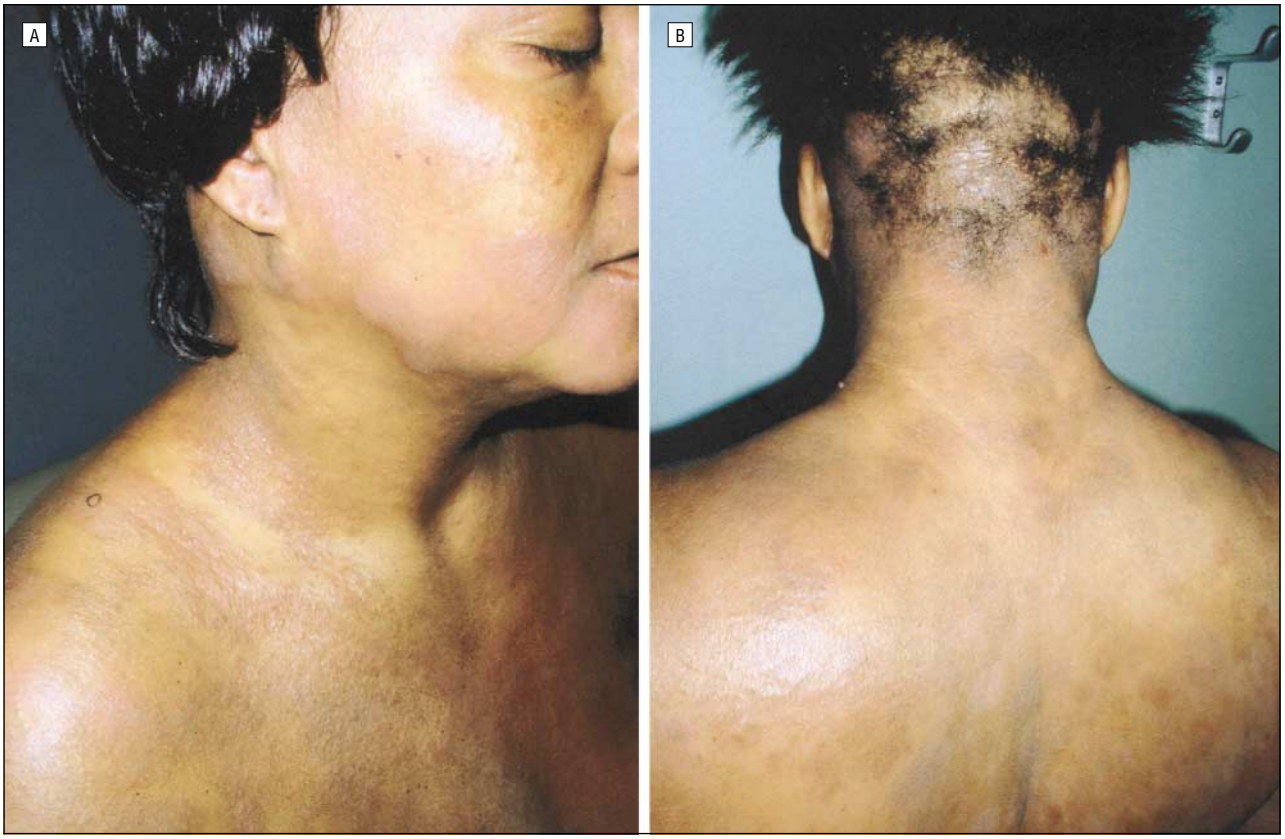

Figure 1. A, Extensive plaques and tumors involving the face, neck, and chest before allogeneic hematopoietic stem cell transplantation in patient 2. B, Extensive plaques and tumors involving the neck and back before treatment in patient 2.

ing topical mechlorethamine hydrochloride, PUVA with interferon alfa, temozolomide, and interleukin 2. Eventually, she developed lymphadenopathy, erythroderma, and thick lichenified plaques covering 40% of her body surface area (**Figure 1**). The serum lactate dehydrogenase level was elevated, and Sézary cells were detected in her blood (20% of total lymphocytes and an absolute count of 980 cells/mL). Lymph node biopsy findings were positive for T-cell lymphoma (histologic grade LN3), reaching stage IVA. After conditioning with cyclophosphamide (120 mg/kg) with mesna, total-body irradiation (1200 rad [12 Gy]), and etoposide therapy (30 mg/kg), she received an allogeneic HLA-matched unmanipulated sibling bone marrow with CD34-enriched peripheral blood stem cell transplant from her sister. She developed mild gastrointestinal tract (grade 1) and skin (grade 2) GVHD that resolved with use of mycophenolate mofetil, a corticosteroid, and cyclosporine (**Figure 2**). Skin biopsy findings at that time were positive for GVHD (histologic grade 2), with no evidence of MF. Mild and transient hypertension with subclinical heart failure resolved with appropriate management. The patient has been in complete remission, free of skin lesions, Sézary cells, or signs of GVHD, since transplantation more than 15 months ago (**Figure 3**).

CASE 3

A 27-year-old African American woman presented with widespread patches, plaques, and tumors involving approximately 35% (T3) of her body surface area (stage IIB).

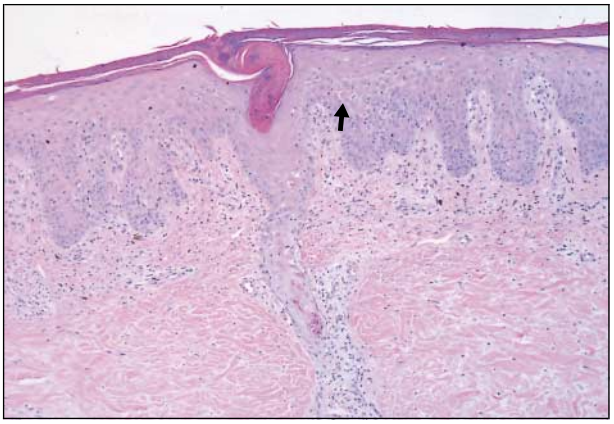

Figure 2. After allogeneic hematopoietic stem cell transplantation, patient 2 developed an acute episode of patches of graft-vs-host disease. The slide shows an interface infiltrate with occasional necrotic keratinocytes (arrow) but no evidence of atypia (hematoxylin-eosin, original magnification ×100).

Skin biopsy samples showed MF large cell type, and a clone was identified by gamma T-cell receptor gene PCR (**Figure 4**). Rare Sézary cells (<5%) were noted in peripheral blood. She soon developed lymphadenopathy, and a nodal biopsy specimen was positive for T-cell lymphoma (stage IVA). With time, the patient became refractory to multiple treatments, including PUVA with interferon alfa, 6 cycles of CHOP (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) and 2 cycles of 9-aminocamptothecin. Conditioning with cyclophosphamide (200 mg/kg) and total-

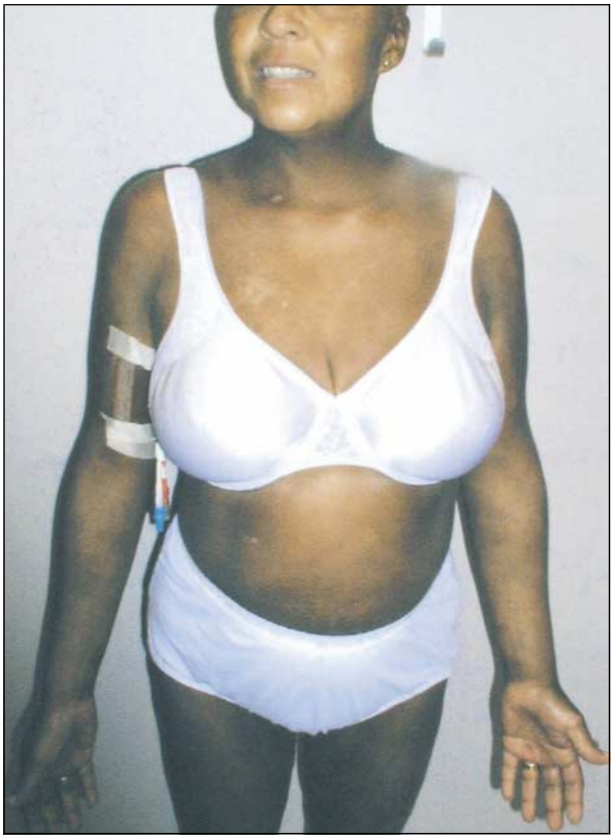

Figure 3. Patient 2 had complete resolution of the lesions after chemoablation, radiation therapy, and allogeneic hematopoietic stem cell transplantation.

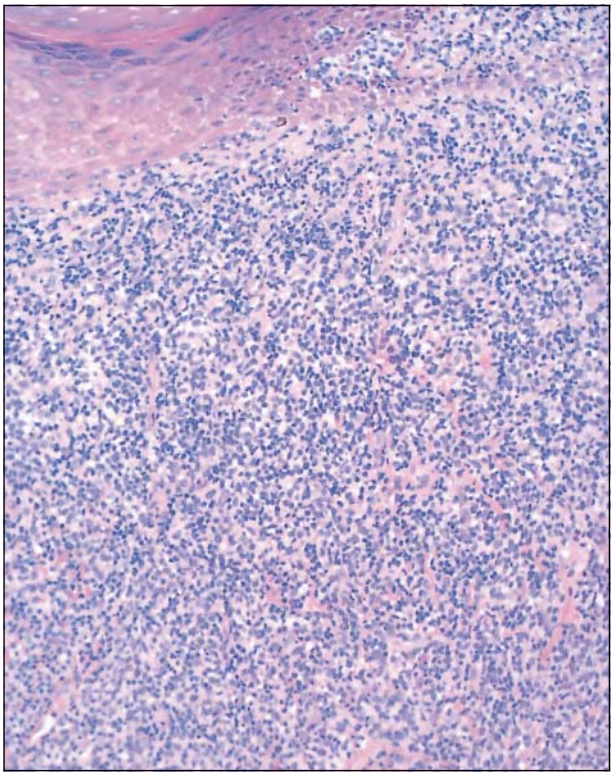

Figure 4. Skin biopsy sample of a tumor from patient 3 showing a dense infiltrate of large and atypical cells (hematoxylin-eosin, original magnification ×400).

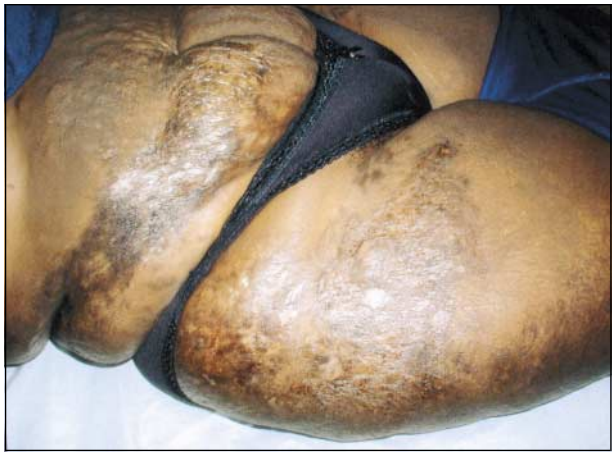

Figure 5. Patient 3 is shown with a large patch of chronic graft-vs-host disease, lichenoid type, involving the thigh.

body irradiation (1200 rad) was followed by allogeneic HLA sibling transplantation. The posttransplantation course was complicated by GVHD of the gastrointestinal tract and liver (grade 2), which resolved with prednisone treatment. Asymptomatic cytomegaloviremia responded to ganciclovir administration. The patient was in complete remission for 9 months when new small papules and plaques on the chest and right thigh were noted. The skin biopsy specimen confirmed the recurrence of MF large cell type, and the T-cell clone was again detected by PCR and Southern blot analysis. Because there was no evidence of GVHD, prophylactic immunosuppression with cyclosporine was discontinued. Within 1 month, the MF plaques resolved and were replaced by lichenoid scaly patches (**Figure 5**). Repeated skin biopsy specimens obtained from the site of previous MF relapse showed lichenoid changes of chronic GVHD without evidence of T-cell atypia or T-cell receptor clonality by PCR. Subsequently, a new onset of small plaques and papules improved with the reinfusion of donor lymphocytes. Resolution of one of the lesions was also corroborated by a negative skin biopsy result. Five years after the allogeneic HSCT, the patient continues to develop occasional small papules and small patches of MF, which respond to topical treatments with mechlorethamine hydrochloride ointment, imiquimod gel, or spot electron beam radiation (**Figure 6**). Surveillance visits with routine computed tomographic scans and blood examination have been negative.

COMMENT

In the past decade, major advances have occurred in the treatment of CTCL. Despite the encouraging results obtained with use of immune-modulating agents and targeted chemotherapy, most patients with advanced CTCL eventually become refractory to treatment and die of complications of the disease, such as infection, as a consequence of the relentless deterioration of the immune status.

Bone marrow transplantation after ablative chemotherapy and irradiation has proved to be an effective curative therapy in various lymphoproliferative and myelo-

proliferative disorders. However, only a few case reports and small series have been published on the effect of HSCT in CTCL.

Autologous bone marrow transplantation has the advantage of being a safe procedure with low treatment-related morbidity and mortality rates, but the results in CTCL have been disappointing. Complete clinical remission was achieved in most cases, but the benefit was short-lived, with rapid relapse (**Table 1**). Hence, although MF is responsive to dose-intense chemotherapy, it is not curable by autologous HSCT. The relapse may be attributed to reinfusion of tumor cells contaminating the autologous graft or failure of high-dose chemotherapy to totally eradicate residual disease. The quick relapse emphasizes a critical factor: the inability of the reinfused and deteriorated host immune system to fight the malignant T-cell process. The high relapse rate of CTCL after chemotherapy and autologous transplantation is consistent with the rates noted in other low-grade lymphomas.[6]

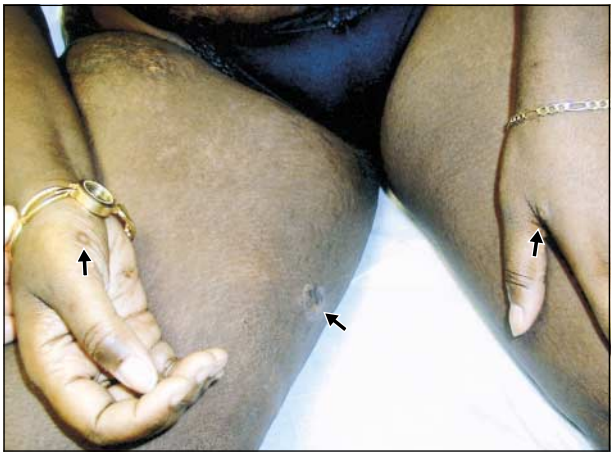

Figure 6. Patient 3 is shown with few recurrent papules (arrows) of mycosis fungoides involving both hands and the right thigh. The lesions resolved with topical treatments.

Because allogeneic transplantation is capable of inducing long remissions in low-grade lymphomas with a lower relapse rate than autologous transplantation, we reasoned that CTCL could respond similarly.[13,14] Allogeneic transplantation from a healthy donor not only eliminates the potential of graft contamination by tumor cells but also provides an immunologic antitumor effect owing to adoptive transfer of donor leukocytes with the allograft. The reconstruction of an effective immune system is therefore pivotal for the treatment's success. An allogeneic graft-vs-tumor effect is best documented in leukemias and is often referred to as a GVL effect. A GVL effect has also been documented in other hematologic conditions. Indeed, chronic myelogenous leukemia, myeloma, and low-grade lymphomas are curable by allogeneic, but not autologous, transplantation. Evidence supporting the potent immunologic effect of GVL in preventing relapse includes (1) lower relapse rates with increasing severity of GVHD, (2) increased relapse rates with T-lymphocyte depletion of the donor graft,[15] (3) increased relapse rates in identical twin donor transplantations with a perfect match but without GVHD,[16] and (4) remission after successful reinduction with donor lymphocyte infusion when the initial allogeneic HSCT had failed.[17] Patient 3 demonstrates that even when relapse occurs after allogeneic transplantation, withdrawal of immunosuppressive therapy or even donor lymphocyte infusion could be an acceptable therapeutic option to treat residual or recurring disease.

The efficacy of donor lymphocyte infusion varies according to the type of leukemia. For example, chronic myelogenous leukemia relapse in the chronic phase responds better than acute leukemia. Whether this difference in remission rates is due to intrinsic immunologic variability between leukemias or differences in growth rates, with faster-growing leukemias not responding as well, is unknown. Nevertheless, the ability of the donor cytotoxic T cells to recognize host and tumor antigens resulting in reinduction underscores the importance of donor immunity in disease remission.[18]

Table 1. Autologous Hematopoietic Stem Cell Transplantation in Patients With Cutaneous T-Cell Lymphoma (CTCL)*

Study, Year	Type of CTCL	Response	Results/Length of Remission/Comments
Olavarria et al,[7] 2001	MF	Complete	Relapse/2 mo
Russel-Jones et al,[8] 2001	MF	Complete	Relapse/14 mo
	MF	Complete	Relapse/12 mo
	MF	None	Relapse/no remission/died
	MF	Complete	Relapse/9 mo
	MF	Complete	Relapse/2 mo/died
	MF	Complete	Relapse/4 mo/died
	MF	Complete	No relapse/10 mo
	MF	Complete	Relapse/1 mo/died
Ferra et al,[9] 1999	MF	Complete	No relapse/22 mo
Sterling et al,[10] 1995	SS (erythrodermic MF)	Partial	NA
Bigler et al,[11] 1991	MF	Complete	No relapse/>1 y
	MF	Complete	No relapse/>1 y
	MF	Complete	Relapse/<100 d
	MF	Complete	Relapse/<100 d
	MF	Complete	Relapse/<100 d
	MF	NA	NA
Chen et al,[12] 1986	MF	Complete	Relapse/6 wk/died

*MF indicates mycosis fungoides; SS, Sézary syndrome; and NA, not available.

Table 2. Allogeneic Hematopoietic Stem Cell Transplantation in Patients With Cutaneous T-Cell Lymphoma (CTCL)*

Study, Year	Type of CTCL	Results/Length of Remission/Comments
Present study	MF	No relapse/>15 mo
	MF	No relapse/>4½ y
	MF large cell type	Limited cutaneous relapse/9 mo[20]
Molina et al,[21] 1999	SS (erythrodermic MF)	No relapse/3 y
Koeppel et al,[22] 1994	MF	Limited cutaneous relapse/ 6 y

*All patients experienced a complete response. MF indicates mycosis fungoides; SS, Sézary syndrome.

If the major advantage of allogeneic transplants is the high response rate achieved by the GVL effect, the major disadvantage is also attributed to the same cell-mediated immune system acquired with the graft, which results in the damage of some of the host epithelial organs (ie, skin, liver, and gastrointestinal tract). Allogeneic transplant patients have a higher risk of treatment-related mortality, particularly when the donor is unrelated. Graft-vs-host disease in allotransplants results in mortality nearing 20%.[1] Although there are some reports of patients developing GVL without GVHD,[19] there seems to be a direct relationship between GVHD and GVL. All patients in our study had mild forms of GVHD. In addition to patient 3 in the present study, who has been described in a previous publication,[20] there have been 2 single case reports of allogeneic HSCT in CTCL (**Table 2**). Koeppel et al[22] described a 21-year-old woman with CTCL stage IVA; 6 years after transplantation, the patient was in remission. However, during the 6 years of follow-up, she had 2 episodes of localized cutaneous recurrence, which resolved with localized irradiation and topical corticosteroid treatment.[22] Because chimerism was proved by cytogenetics, this case confirms our impression that even in the event of partial remission, the downgrading of CTCL with myeloablative therapy followed by allogeneic HSCT and the powerful GVL effect can prevent the malignant T-cell process from tumor progression. The other case report[21] was a young woman with refractory Sézary syndrome who was disease free 3 years after allogeneic transplantation.

For young patients with advanced CTCL (tumor or large cell transformation or stage III and IV) who have not responded to standard treatment options and who have a suitable donor, the potential benefits of matched sibling allogeneic HSCT, in our opinion, outweigh the serious potential complications of the procedure. Furthermore, significant advances in the management of acute and chronic GVHD with modalities such as extracorporeal photopheresis, anti–tumor necrosis factor α therapies, and mycophenolate mofetil treatement may increase the appeal of allotransplants in CTCL.[23] An alternative approach in the future treatment of lymphoproliferative disorders with allogeneic HSCT may be the use of low-dose, nonmyeloablative protocols, also known as minitransplants. This strategy spares the high morbidity and mortality of allotransplants. Although this treatment approach without chemoablation is not designed to eradicate the lymphoma, the hematopoietic graft creates a chimeric marrow with a powerful GVL effect. The results of minitransplants in patients who initially were not eligible for a standard allotransplant protocol have been encouraging, with reported complete remission of 67% in patients with chronic lymphocytic leukemia.[24] The minitransplant strategy may eventually offer some hope for the many patients with CTCL who are presently ineligible for allogeneic HSCT because of their advanced age (>60 years) or suboptimal renal or cardiac performance. Furthermore, Molina et al[25] recently presented an abstract that included a patient with advanced CTCL who achieved complete remission after a "reduced-intensity" regimen of fludarabine phosphate and melphalan with allogeneic HSCT. That case further supports the potential benefit of the GVL effect in the treatment of CTCL. Similar to patient 1 in the present study, other studies of patients with durable complete remissions after allogeneic HSCT are encouraging and show the potential for cure in advanced CTCL.[25] The advantages of allogeneic transplantation include low relapse rates, improved disease-free survival, and GVL with the option of donor lymphocyte infusion therapy in case of recurrence.[22,26-28]

The patients described herein demonstrate the important role of an effective immune system capable of fighting the tumor cells during the treatment of CTCL. Allogeneic HSCT provides hope for a curative treatment modality for patients with advanced and refractory CTCL.

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News and Notes

The Sixth World Conference on Melanoma will be held in Vancouver, British Columbia, September 2-9, 2005. The conference will attract more than 2000 international researchers and experts in the prevention, treatment, and management of melanoma. Delegates will include immunologists, pathologists, epidemiologists, and clinicians. For more information please contact the Sixth World Conference on Melanoma Secretariat c/o Venue West Conference Services Ltd, 645-375 Water St, Vancouver, British Columbia, Canada V6B 5C6; phone: (604)-681-5226; fax: (604)-681-2503 (e-mail: congress @venuewest.com; Web Site: www.worldmelanoma.com).