Bone Marrow Transplantation (2001) 28, 97–99

www.nature.com/bmt

Case report

Beneficial effect of intravenous lidocaine in cutaneous chronic graft-versus-host disease secondary to donor lymphocyte infusion

JC Voltarelli[1], H Ahmed[2], EJA Paton[1], ABPL Stracieri[1], P Holman[2], A Bashey[2], M Coutinho[1], BP Simoes[1], ED Ball[2] and E Carrier[2]

[1]*Bone Marrow Transplantation Unit, University Hospital, School of Medicine of Ribeirão Preto, University of São Paulo, Brazil; and* [2]*Blood and Marrow Transplant Division, University of California, San Diego School of Medicine, La Jolla, CA, USA*

Summary:

We report two cases of refractory chronic graft-versus-host disease after donor lymphocyte infusions in which the skin lesions improved dramatically with the use of intravenous pulses of lidocaine. This form of therapy has been used successfully for the cutaneous involvement of scleroderma and may have vasodilator and anti-inflammatory effects. *Bone Marrow Transplantation* (2001) **28,** 97–99.
Keywords: chronic GVHD; lidocaine; donor lymphocyte infusion

Donor lymphocyte infusion (DLI) is a very promising immunotherapeutic modality of treatment for relapse of malignancy after hematopoietic stem cell transplantation (HSCT) (reviewed in Ref. 1). However, it is associated with significant morbidity and mortality due to marrow aplasia and graft-versus-host disease (GVHD). In a survey of 140 patients treated with DLI for relapse of a variety of malignant diseases in 25 North American centers 75 of 125 (60%) evaluable patients developed acute GVHD (28 with grades III or IV) and 51 out of 84 (61%) developed chronic GVHD (24 with limited and 27 with extensive forms).[2] In another series of 22 patients with chronic myelogenous leukemia, nine (41%) developed chronic GVHD (five limited, four extensive forms).[3] In the first study there was a correlation between clinical response to DLI and development of acute and chronic GVHD, while in the latter one low doses of DLI could induce a graft-versus-leukemia effect without GVHD.

Chronic GVHD associated with allogeneic HSCT or DLI seems to have a similar clinical picture[4] and may cause significant disability and deterioration of quality of life, in part because of sclerodermatous skin changes leading to severe contractures.[5] These lesions are poorly responsive to conventional immunosuppression or to alternative therapies for GVHD such as thalidomide, mycophenolate mofetil and tacrolimus, etretinate, PUVA (psoralen plus ultraviolet irradiation) and extracorporeal phototherapy. Spontaneously occurring systemic sclerosis shares the autoimmune pathophysiology and poor treatment response with chronic GVHD[6] and local anesthetics were one of many treatments attempted for the skin manifestations of systemic sclerosis.[7]

We report here two cases of sclerodermatous cutaneous chronic GVHD after DLI, which responded dramatically to intravenous administration of lidocaine.

Correspondence: Dr JC Voltarelli, Bone Marrow Transplantation Unit, Hospital das Clinicas, Campus of the University of São Paulo, 14048–900 Ribeirão Preto, Brazil
Received 8 November 2000; accepted 5 April 2001

Case reports

Patient 1

The first patient, an 11-year-old boy, received an HLA-identical bone marrow transplantation donated by his sister at the University Hospital of the School of Medicine of Ribeirão Preto, Brazil in September 1995 for an acute biphenotypic leukemia in first complete remission. The conditioning regimen was busulfan 16 mg/kg and cyclophosphamide 120 mg/kg and GVHD prophylaxis was methotrexate plus cyclosporine. The early post-transplant course was uneventful without acute GVHD and with establishment of full donor chimerism (100% XX). At day +530 post-transplant hematologic relapse was detected in the bone marrow (17% blasts). An infusion of donor peripheral blood lymphocytes containing 1.13×10^8 T cells ($CD3^+$)/kg was given with recombinant IL-2 (6 million U/m^2/day $\times$ 3) followed by α-interferon (3 million U/m^2 3 times a week) both subcutaneously. Three months later, the patient was asymptomatic but there were 16% of blasts in the BM and a second infusion was given with 2.7×10^8 T cells/kg plus recombinant human interleukin-2 (10 million U/m^2/day $\times$ 3). Complete hematological remission was achieved (2% blasts in BM) without development of acute GVHD. Chronic GVHD developed 3 months later involving the skin, oral mucosa and eyes which responded to oral prednisone (1 mg/kg/day), but relapsed when the steroid dose was reduced. After 6 months thalidomide was added (100 mg twice a day) and prednisone was tapered. The liver and lungs were involved, liver function tests showed total

bilirubin 1.19 mg/dl, SGOT 202 U/l, SGPT 339 U/l, alkaline phosphatase 779 U/l and pulmonary function tests showed FEV1 43% of predicted, FEV1/FVC 56%. Sclerodermous skin lesions appeared and led to contractures. Four monthly pulses of i.v. lidocaine (400 mg diluted in 250 ml normal saline/day × 5 days) were administered followed by two pulses in 6 months (total of six pulses) without any side-effects. After the first pulse the appearance of skin lesions improved significantly, thalidomide was discontinued, and after the fourth pulse the range of movements increased in the elbows (33%), wrists (44%) and knees (21%). However, pulmonary and liver lesions persisted and alternate day cyclosporine (5 mg/kg/day)/prednisone (1 mg/kg/day) was started, improving the liver function (bilirubin 0.38 mg/dl, SGOT 43 U/l, SGPT 40, alkaline phosphatase 375 U/l), but not the pulmonary function (FEV1 26%, FEV1/FVC 41%). At day +1445 post-BMT (+780 post-DLI) a second hematologic relapse was diagnosed (45% blasts in BM, 58% XY) along with worsening of pulmonary GVHD. Immunosuppression was discontinued and the patient was treated with daunorubicin plus Ara-C, developed marrow aplasia and died of respiratory insufficiency on day +1473.

Patient 2

The second patient is a 20-year-old woman with chronic myelogenous leukemia in chronic phase who was transplanted in March 1993 with bone marrow from her HLA-identical sister at the Children's Hospital in San Diego and subsequently was treated at the University of California San Diego Medical Center. She developed grade II acute GVHD after the BMT and was treated with CsA and prednisone 1 mg/kg/day. Hematological relapse was diagnosed (peripheral blood WBC: 33 000/μl, BM: M:E ratio 10) on day +1350 post BMT and she received hydroxyurea (1.5 g/day), 10^8 peripheral blood T cells/kg from the marrow donor and α-interferon (5 million U/day s.c.) 4 weeks after DLI. There was a hematological response (WBC 9000/μl), but the patient developed grade III skin GVHD expressed by generalized maculopapular rash along with liver involvement (total bilirubin 2.0 mg/dl, SGOT 233 U/l, SGPT 232 U/l, alkaline phosphatase 170 U/l, confirmed by liver biopsy). She was treated with prednisone (1 mg/kg/day) plus cyclosporine (5 mg/kg/day) which improved the liver function tests, but the skin lesions became sclerodermatous involving the torso, upper and lower extremities, face, scalp and back in 6 months. The lesions progressed to open wound ulcers over her lower extremities (Figure 1). She underwent PUVA therapy with little improvement and was started on thalidomide 50 mg twice a day at day +1860. Over the next 3 months the skin lesions showed a gradual healing allowing the prednisone dose to be tapered, but the chest skin became very tight and thalidomide was lowered to 50 mg every other day and discontinued 6 months later. The skin remained very dry and fibrotic and the patient experienced severe pain in her lower extremities and abdomen. She underwent extensive surgical and tomographic evaluation for abdominal pain which did not disclose a source. Lidocaine was started on day +1920 at the same dose reported for patient 1. After the first cycle the pain improved dramatically and after three cycles marked softening of skin lesions was observed over the chest wall, breast and groin. No side-effects were observed during or after lidocaine infusions. She received 12 monthly pulses of lidocaine and continued to improve, defined as softening of the skin, absence of skin ulcerations, decreased pain and the ability to discontinue pain medications (Figure 1). Sclerodermatous lesions were cleared from the face (100% surface area), neck (80%), hands

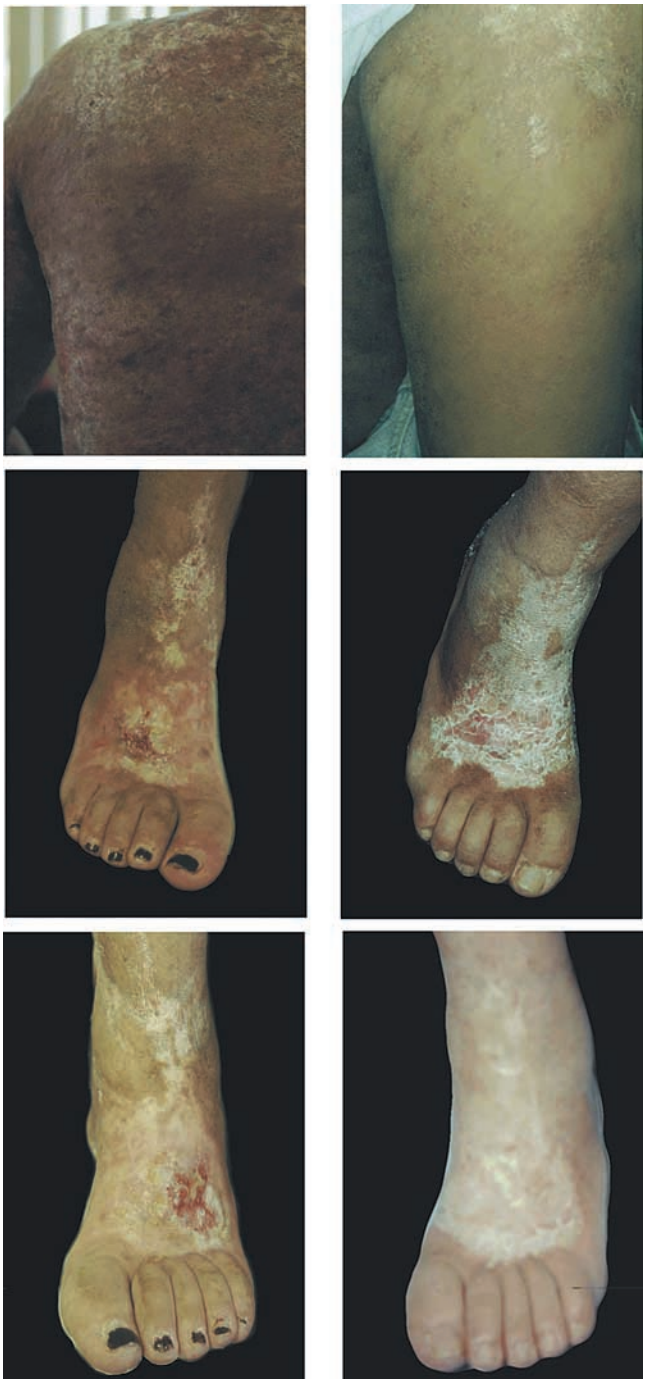

Figure 1 Cutaneous lesions of chronic GVHD in the chest wall and foot dorsum of patient 2 before (left) and after (right) 12 months (upper, middle) and 30 months (lower) of starting lidocaine pulses.

(100%), arms (40%), legs (60%) and abdomen (20%). Lidocaine pulses were spaced to every 3 months, but the skin lesions worsened and in November 1999 (day +2400) the pulses were returned to monthly intervals which continuously improved the skin lesions. She received a total of 26 pulses and currently is receiving lidocaine 400 mg twice a month.

Discussion

Chronic GVHD secondary to stem cell transplantation or to adoptive immunotherapy is caused by alloreactive $CD4^+$ T helper cells which infiltrate the skin, mucosal surfaces and visceral organs and cause upregulation of inflammatory cytokines and fibrosis. The clinical and histopathologic picture of chronic GVHD is similar to that of systemic sclerosis and some other systemic autoimmune diseases and recently the pathogenesis of systemic sclerosis was linked to a form of chronic GVHD induced by alloreactive fetal lymphocytes which have crossed the placental barrier during pregnancy.[6]

Treatment modalities for either chronic GVHD or systemic sclerosis have generally been unsatisfactory. Immunosuppressive therapy with cyclosporine and corticosteroids causes a high incidence of opportunistic infections and significant mortality in chronic GVHD while less aggressive forms of immunosuppression employed in spontaneous systemic sclerosis usually fail to deter the progression of the disease. This fact led to the utilization of a variety of therapeutic approaches in both conditions including PUVA therapy, antifibrotic agents and vasodilators.[8]

Lidocaine is a local anesthetic drug which has been used by systemic routes in the treatment of Raynaud phenomenon[9] and systemic sclerosis.[7] In one of our centers in Brazil we have a large experience in the treatment of systemic sclerosis with intravenous pulses of lidocaine leading to improvement of Raynaud phenomenon in most patients, remarkable softening of skin lesions in about 50% of the patients, but no improvement of esophageal or pulmonary manifestations (Voltarelli *et al*, unpublished). The response is dependent on maintenance of the pulses (every 2–3 months). We have documented by pletismographic measurements that this treatment strategy produces an increase in peripheral arterial blood flow in patients with systemic sclerosis.[7] Alternatively, lidocaine may affect other components of chronic inflammation in GVHD such as collagen secretion, lymphocyte traffic, cytokine production or release, and neutrophil or macrophage activation.[10]

The above-mentioned benefits of lidocaine i.v. pulses in systemic sclerosis prompted us to try this therapeutic approach in two patients with severe and refractory skin chronic GVHD secondary to DLI. The rapid improvement of the skin lesions and symptoms observed in both patients suggests that in cutaneous chronic GVHD lidocaine mediates the same vasodilator effect seen in systemic sclerosis. In the first patient, the marked regression of skin lesions with lidocaine did not preclude the progression of pulmonary GVHD indicating that the drug probably lacks any significant effect on systemic lesions. In the second patient, there was a clear association between scheduling of lidocaine pulses and clinical improvement. Thus, benefits of lidocaine shown in these two cases and in many patients with systemic sclerosis without any side-effects indicate that the drug deserves clinical trials in chronic GVHD affecting the skin after DLI or allogeneic stem cell transplantation.

Acknowledgements

We are grateful to Dr Mary E Flowers for reviewing the manuscript, Ms Elisa Vendramini for assessing range of movements of patient 1, and for FAPESP (Proc 98/11981–0), CNPq, FAEPA/HCRP and FUNDHERP for financial support in Brazil.

References

1 Dazzi F, Goldman J. Donor lymphocyte infusions. *Curr Opin Hematol* 1999; **6**: 394–399.
2 Collins RH, Shpilberg O, Drobyski WR *et al*. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. *J Clin Oncol* 1997; **15**: 433–444.
3 Mackinnon S, Papadopoulos EB, Carabasi MH *et al*. Adoptive immunotherapy evaluating escalating doses of donor leukocytes for relapse of chronic myeloid leukemia after bone marrow transplantation: separation of graft-versus-leukemia responses from graft-versus-host disease. *Blood* 1995; **86**: 1261–1268.
4 Bar BMAM, Schattenberg A, Mesink EJBM *et al*. Donor leukocyte infusions for chronic myeloid leukemia relapsed after allogeneic bone marrow transplantation. *J Clin Oncol* 1993; **11**: 513–519.
5 Caballero MJ, Fernandez-Herrera J, Cordoba-Guijarro S *et al*. Sclerodermatous graft-versus-host disease after donor leukocyte infusion. *Br J Dermatol* 1998; **139**: 889–892.
6 Famularo G, Simone D. Systemic sclerosis: from autoimmunity to alloimmunity. *South Med J* 1999; **92**: 472–476.
7 Zollner RL, Dantas RO, Godoy RA. Treatment of progressive systemic sclerosis with lidocaine hydrochloride: a preliminary study. *Braz J Med Biol Res* 1985; **18**: 620a.
8 Liesveld JL, Duerst RE, Rapoport AP *et al*. Continuous infusion cyclosporine and nifedipine to day +100 with short methotrexate and steroids as GVHD prophylaxis in unrelated donor transplants. *Bone Marrow Transplant* 1999; **24**: 511–516.
9 Van Der Molen HR, Balmus K. Some little known conservative methods of treatment of Raynaud's syndrome. *Phlebologie* 1977; **30**: 199–204.
10 Sinclair R, Eriksson AS, Gretzer C *et al*. Inhibitory effects of amide local anesthetics on stimulus-induced human leukocyte metabolic activation, LTB-4 release and IL-1 secretion *in vitro*. *Acta Anaesthesiol Scand* 1993; **37**: 159–165.