Imatinib as a Potential Treatment for Sclerodermatous Chronic Graft-vs-Host Disease

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

Chronic graft-vs-host disease (GVHD) remains the most common late complication of allogeneic hematopoietic stem cell transplantation (HSCT), despite improvements in its prophylaxis. Although the graft-vs-leukemia effect associated with the development of chronic GVHD may be beneficial in controlling the underlying disease, patients with chronic GVHD are prone to fatal infections owing to multiple abnormalities of their reconstructed immune systems. Infection is the most common cause of death in patients with chronic GVHD. Chronic GVHD may also compromise a patient’s quality of life as a result of long-term immunosuppressive therapy and the symptoms of GVHD itself. Chronic GVHD appears to be one of the major determinants in the survival and quality of life of patients after allogeneic HSCT.1

Sclerodermatous GVHD is a rare form of chronic GVHD, with a prevalence of approximately 3% in patients who have received allogeneic bone marrow transplants. Sclerodermatous GVHD may be generalized or localized. Generalized forms cause considerable functional disability because of reduced mobility. Mortality may be approximately 20% to 40%, owing to extracutaneous involvement, although some series have shown reduced mortality in cases of sclerodermatous GVHD as a result of an enhanced graft-vs-tumor effect.2

REPORT OF A CASE

An 18-year-old man with Philadelphia chromosome–positive chronic myeloid leukemia received a peripheral blood HSCT from a matched unrelated donor after myeloablative conditioning in February 2004. Cyclosporine and a short course of methotrexate (4 doses) were administered as GVHD prophylaxis. On day +12, the patient presented with signs of acute cutaneous GVHD (grade II) that resolved with a course of systemic corticosteroids. Because of several cutaneous GVHD flares and a toxic reaction to cyclosporine therapy, prophylaxis with mycophenolate mofetil was initiated. Despite the prophylactic therapy, in June 2005 a generalized lichenoid eruption developed on the patient’s trunk, upper extremities, and oral mucosa, with widespread postinflammatory hyperpigmentation, characteristic of lichenoid chronic GVHD. On follow-up in March 2006, there were also some shiny plaques with fine wrinkling over the trunk, suggesting lichen sclerosus–like sclerodermoid chronic GVHD. After a few months, new lesions developed, and there were sclerotic plaques with a scaly surface surrounded by diffuse, indurated hyperpigmentation on the lower extremities and some areas of the trunk. A skin biopsy specimen showed epidermal atrophy with a grossly sclerotic dermis composed of expanded bundles of pale hyalinized collagen. Adnexal structures were replaced by dense sclerosis. The dosage of prednisone therapy was increased, and topical treatment with corticosteroids and tacrolimus, 0.1%, was added to the regimen; however, in October 2006, the sclerotic plaques progressed, involving the upper extremities and most of the trunk as well (Figure 1). The skin of these areas could not be pinched, and the patient had severe functional restriction and pain. Photochemotherapy was initiated, with little improvement. At this time, low-dose weekly oral methotrexate therapy (7.5 mg/m²/wk [12.5 mg/wk]) was started, along with plasma volume expanders and physiotherapy, with very few changes in the cutaneous sclerosis. Unfortunately, the patient developed cryptococcal meningoencephalitis, which resulted in a very long hospitalization (4 months), and the methotrexate therapy had to be discontinued. At discharge, the sclerosis of the lower limbs had progressed, causing very severe contractions and mobility restriction, and the patient became wheelchair bound. An alternative treatment was needed.

THERAPEUTIC CHALLENGE

Sclerodermatous chronic GVHD is a disease that is difficult to treat. Therapy with systemic corticosteroids and
immunosuppressants (eg, cyclosporine, tacrolimus, mycophenolate mofetil, methotrexate, and azathioprine) is limited by adverse effects and is often unsuccessful in the management of sclerodermatous GVHD. Also, intensive immunosuppression may contribute to relapse of leukemia or infectious diseases. Treatment options are largely unsatisfactory if conventional immunosuppression fails. Psoralen–UV-A therapy may give some symptomatic benefits, and extracorporeal photopheresis seems to be less efficacious than was previously reported. There are also some anecdotal reports regarding the use of biologic agents (eg, alemtuzumab, infliximab, rituximab, and combination treatment with daclizumab and etanercept), antithymocyte globulin, systemic retinoids, thalidomide, and clofazimine for the treatment of sclerodermatous chronic GVHD, but without consistent efficacy.

SOLUTION

Sclerodermatous chronic GVHD is an immune-mediated disease with a striking resemblance to systemic sclerosis. Recently, the presence of stimulatory autoantibodies against the platelet-derived growth factor receptor (PDGF-R) has been described both in patients with systemic sclerosis and in patients with extensive chronic GVHD. The authors were able to identify functionally active autoantibodies against PDGF-R in serum samples from patients with extensive chronic GVHD. The finding that stimulatory autoantibodies against the anti-PDGF-R may be directly responsible for the sclerotic or fibrotic changes in chronic GVHD and involve tyrosine kinase-dependent signaling could provide the rationale for molecular-targeted treatment of chronic GVHD with imatinib mesylate.

Therefore, we decided to start treatment with imatinib mesylate at low doses (100 mg/d) with careful monitoring. This treatment has been well tolerated, without any adverse effect, and after 12 months of follow-up, we have seen a progressive and substantial improvement in the hardening and stiffness of the patient’s skin. At present, there are no active lesions, and the skin of the trunk is now soft to palpation and can be easily pinched. The patient has slowly improved his functional capacity and mobility, although he still needs a wheelchair or crutches mainly because of the severe muscular atrophy that remains after his prolonged stay in the intensive care unit.

COMMENT

Imatinib mesylate (Glivec and Gleevec; Novartis, Basel, Switzerland) is a potent selective inhibitor of the tyrosine kinases ABL, PDGF-R alfa and beta, c-KIT, ARG, and LCK. It has proven clinical efficacy in the treatment of the following malignant neoplasms, which are characterized by constitutive activation of these tyrosine kinases: chronic myeloid leukemia, Philadelphia chromosome–positive acute lymphocytic leukemia, dermatofibrosarcoma protuberans, myeloproliferative disorders due to chromosomal rearrangements in the PDGF-R locus, and gastrointestinal stromal tumors with mutations in c-KIT. Imatinib is increasingly being used as a means to prevent or treat relapse of Philadelphia chromosome–positive leukemias after allogeneic HSCT.

Since GVHD is predominantly T-cell mediated, and imatinib appears to have powerful suppressive effects on T-cell proliferation and function, it seems reasonable that the use of imatinib after allogeneic stem cell transplantation may result in a reduced graft-vs-host effect. Also, it has been recently demonstrated that patients with systemic sclerosis have serum stimulatory autoantibodies that target PDGF-R. These antibodies trigger an intracellular...
lar loop, involving Ha-Ras extracellular signal-regulated kinase 1/2 reactive oxygen species, which leads to increased collagen gene expression and myofibroblast phenotype conversion of normal human primary fibroblasts. In a later study, these stimulatory autoantibodies were found in patients with extensive chronic GVHD.

It has also been demonstrated that imatinib strongly reduces the synthesis of the major extracellular matrix proteins COL1A1, COL1A2, and fibronectin 1 in cultured dermal fibroblasts from patients with systemic sclerosis. Furthermore, imatinib therapy efficiently suppressed the development of fibrosis in experimental dermal fibrosis in vivo. It has been speculated that blocking PDGF-R activation with imatinib might be of clinical benefit in patients with systemic sclerosis and chronic GVHD. Effects of imatinib on immune reconstitution and T-cell function may be especially relevant in the setting of allogeneic transplantation, in which the regulation of immune functions in the posttransplantation period is especially critical and directly affects morbidity and mortality. The use of imatinib directly inhibits T-cell receptor signaling, and this effect might enhance the effects of therapy with immunosuppressive drugs.

In conclusion, we report a case of severe sclerodermatous chronic GVHD that was successfully treated with imatinib. To our knowledge, our patient represents the first case of chronic GVHD treated with imatinib reported in the literature. We cannot rule out that the improvement seen in this case may be attributable to the natural evolution of the disease; however, the striking progression of sclerotic lesions that our patient experienced before the introduction of imatinib therapy makes us doubt it. Considering the potent antifibrotic effects of imatinib therapy via the inhibition of PDGF-R, the low rate of adverse effects, and the favorable clinical experience in other diseases, imatinib could be a promising candidate for the treatment of fibrotic diseases such as sclerodermatous chronic GVHD and systemic sclerosis. The results of this single case are promising, but double-blind, controlled studies will be needed to evaluate the efficacy of imatinib therapy for chronic GVHD.

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Figure 2. Major improvement of the sclerotic features on the legs and trunk in October 2007, after 7 months of imatinib therapy. A, Abdomen (the skin can easily be pinched). B, Anterior aspect of the legs.

**Paul Langerhans: A Tribute to an Admirable Life in Science**

Paul Langerhans was born in Berlin, Germany, in 1847, the son of a well-known physician. He studied medicine at Friedrich Schiller University of Jena, Jena, Germany, and at the University of Berlin and was a pupil of Rudolph Virchow. He made an outstanding contribution to medicine by describing Langerhans cells while he was a 21-year-old undergraduate student. Because these branched cells, which were interspersed throughout the epidermis, were demonstrated by a stain for which nervous tissue has a particular affinity, ie, gold chloride, he suggested that they could be intraepidermal receptors of extracutaneous signals to the nervous system. Today, the precision of his observation and his description of the cells seem incredible, when his drawings of 1868, which were made with the use of a primitive light microscope, are compared with the reproductions that can now be obtained with immunofluorescence. These cells were an enigma to dermatologists for more than a century before their immunologic function and importance were recognized.

Langerhans also provided the first careful and detailed description of the microscopic structure of the pancreas, which hitherto had been regarded as no more than a sort of supplementary salivary gland. Aside from the acinar component, he perceived small clumps of cells that lacked secretary granules or any ductal connection. He described 9 different types of cells throughout the pancreas and suspected that these islands might exert an endocrine effect. Another important contribution, which was developed in Virchow’s laboratory, dealt with the macrophage system. Langerhans and Hoffmann studied the intravital storage of cinnabar, which was injected intravenously into rabbits and guinea pigs. They were able to show that cinnabar was taken up by white blood corpuscles but never by red. They also demonstrated deposits of cinnabar in fixed cells of the bone marrow, capillaries, and connective tissue of the liver. This was one of the pioneering investigations that later led to Aschoff’s concept of the reticuloendothelial system. Moreover, Langerhans carried out original investigations into the etiology of tuberculosis and the pathophysiology of leprosy and was involved in zoological studies that resulted in the publication of articles on the hearts of amphibious animals and the eyes of lampreys, among many others. After settling on his “Portuguese prison island” of Madeira because of pulmonary tuberculosis, he did not stop his scientific work. He continued his zoological studies, which led to the discovery of a large number of new species, most of them bearing the eponym of Langerhans, as well as to a series of publications that represent a remarkable contribution to the literature on invertebrates. He practiced medicine in the capital of Madeira, Funchal, where he died of a kidney infection in 1888.

We are deeply indebted to this great man, who significantly advanced our understanding of investigative dermatology during his short but prolific life of 41 years.

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