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ORIGINAL ARTICLE

Efficacy of imatinib mesylate in the treatment of refractory sclerodermatous chronic GVHD

L Magro[1], B Catteau[2], V Coiteux[1], B Bruno[1], J-P Jouet[1,2,3] and I Yakoub-Agha[1,2,3]

[1]*Service des Maladies du Sang, Lille, France;* [2]*Service de Dermatologie, Lille, France and* [3]*EA2686, CHRU, Lille, France*

Treatment of sclerodermatous chronic GVHD (cGVHD) remains disappointing. Imatinib mesylate enables selective, dual inhibition of the transforming growth factor β (TGFβ) and PDGF pathways. Recently, the drug's effects on fibroblasts have been reported in both *in vitro* and *in vivo* studies. The inhibition of fibroblast growth and decreased collagen production in dermal fibroblasts is thus a logical therapeutic approach. Two patients who developed refractory sclerodermatous cGVHD following allo-SCT received imatinib mesylate at the dose of 400 mg/day. In both patients, the scleroderma symptoms disappeared within 3 months of initiation of the treatment. At the time of this report, the two patients were both alive and had a very good skin response. This report shows that imatinib is effective in patients with refractory sclerodermatous cGVHD. Considering its well-documented clinical profile in other diseases, imatinib is a promising candidate for the treatment of sclerodermatous cGVHD.
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Introduction

Allo-SCT is a curative approach that has been used in a wide range of otherwise fatal hematological diseases.[1–5] However, chronic GVHD (cGVHD) is a major cause of morbidity and mortality in long-term allo-SCT survivors. This complication can have features of autoimmune collagen vascular disease, with clinical manifestations similar to those of autoimmune scleroderma and systemic lupus erythematosus. Indeed, sclerodermatous cGVHD is one of the most severe forms of the condition and has very disappointing treatment outcomes. A variable degree of success in the reduction of cGVHD incidence and/or severity has been obtained with the use of various immunosuppressive drugs but the sclerodermatous form of the disease is often refractory to standard treatment approaches.[6–8]

Imatinib mesylate is a clinically well-tolerated tyrosine kinase inhibitor and is effective in patients with CML and those with stromal gastrointestinal tumors.[9–11] The drug exerts selective, dual inhibition of the transforming growth factor β (TGFβ) and PDGF pathways.[12] Recently, its effects on fibroblasts have been described in both *in vitro* and *in vivo* studies.[13–16] Here, we report on our experience in the first two patients to receive imatinib mesylate as an antifibrotic treatment of refractory sclerodermatous cGVHD. Table 1 summarizes the patients' characteristics and transplant procedures.

Patients and methods

In November 1996, a 45-year-old female patient underwent myeloablative allo-CST for chronic-phase CML. After 8 months, she developed limited cutaneous cGVHD, which resolved after dermal corticosteroid treatment. In 1999, she was prescribed CYA and corticosteroids for sclerodermatous cGVHD. Despite the fact that the patient did not experience full regression of the cGVHD, immunosuppressive treatment was discontinued in 2000 and INF-α was given following a molecular relapse of the CML. After failing to respond to INF-α treatment, the patient received donor lymphocyte infusions in December 2001 and June 2002. Unfortunately, donor lymphocyte infusion not only failed to induce CML disease remission but was also responsible for re-activating the sclerodermatous cGVHD (Figure 1a1). No immunosuppressive treatment was given but the patient was prescribed imatinib at 400 mg/day because of the CML molecular relapse. After 3 months, the patient displayed CR of both cGVHD and CML. At the time of this report (1 February, 2008), she is still alive, off immunosuppressors and in remission with imatinib. She now has only limited oral lichenoid cGVHD (Figure 1a2).

In January 1998, our second patient (a 26-year-old male) underwent myeloablative allo-CST for chronic-phase CML. Although CML relapse never occurred, the patient received four different types of immunosuppressive therapy for refractory sclerodermatous cGVHD from June 1998 to November 2007, at which point 400 mg/day imatinib mesylate was added to the ongoing immunosuppressive

Correspondence: Dr I Yakoub-Agha, Service des Maladies du Sang, CHRU de Lille, UAM allogreffes de CSH, Lille, CEDEX F-59037, France.
E-mail: i-yakoub-agha@chru-lille.fr
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Table 1 Initial characteristics of, and transplantation procedures and treatments received by, the two patients prior to initiation of imatinib mesylate

	Patient 1	*Patient 2*
Age at allo-SCT	34 years	26 years
Year of allo-SCT	1996	1998
Conditioning	CY and TBI-12	CY and TBI-12
Donor and source of SCs	Sibling; marrow	Unrelated; marrow
Acute GVHD	(d + 17) Grade-I cutaneous	(d + 15) Grade-II cutaneous Resolved (steroids) (d + 34) Grade-III cutaneous/liver Resolved (steroids)
Chronic GVHD	(M + 8) Limited, lichenoid Resolved (steroids) (M + 25) Sclerodermatous VGPR (CsA and steroids) (M + 30) Molecular relapse of CML Failure (IFNα) (M + 49) First DLI 107 $CD3^+$/kg (M + 55) Second DLI 107 $CD3^+$/kg (M + 59) Extensive, sclerodermatous	(M + 5) Limited, sclerodermatous Failure (CsA and steroids) (M + 7) Extensive, sclerodermatous Failure (addition of azathioprine) (M + 21) Extensive sclerodermatous Failure (thalidomide) (M + 24) Extensive sclerodermatous Brief improvement (MMF) (M + 28) Extensive sclerodermatous Failure (MMF and everolimus)
Initiation of imatinib mesylate	(M + 60)	(M + 35)

Abbreviations: d = day post transplantation; DLI = donor lymphocyte infusions; M = month post transplantation; MMF = mycophenolate mofetil; VGPR = very good partial response.
CY was administered at a dose of 60 mg/kg/day for 2 consecutive days; TBI-12, fractionated TBI at the dose of 12 Gy.

regimen as an antifibrotic treatment. At the time of this report, he is alive and has a very good partial cGVHD response with a very good improvement in the quality of life. Figure 1 shows his skin status before treatment with imatinib mesylate (panels b1 and c1) and after 3 months (panels b2 and c2).

The two patients were assessed monthly by our multidisciplinary care team. We used the modified Rodnan skin score to assess the extent of skin damage in both patients.[17] Of note, imatinib was well tolerated by the patients.

The incidence of sclerodermatous cGVHD is about 11% in allo-SCT patients.[8] Furthermore, the use of PBSCs obtained from G-CSF-mobilized donors has increased over the last decade. It has recently become clear from both clinical and experimental work that the incidence of extensive cGVHD is higher in recipients of G-CSF-mobilized PBSCs.[18,19]

Discussion

The pathogenesis of chronic GVHD is poorly understood. The skin manifestations of the autoimmune disease systemic sclerosis (scleroderma) are clinically and histologically similar to the cutaneous manifestations of sclerodermatous cGVHD. Both conditions are characterized by excess collagen production. The inhibition of fibroblast growth and decreased collagen production in dermal fibroblasts is thus a logical therapeutic approach. However, patients with sclerodermatous chronic GVHD may fail to improve, either because of worsening cGVHD or simply when there is no improvement in their fibrosis despite stable or reduced GVHD.

Profibrotic cytokines (such as TGFβ and PDGF) have key function in the pathogenesis of scleroderma.[20] Both cytokines are upregulated in the skin of idiopathic scleroderma patients and strongly stimulate matrix synthesis by dermal fibroblasts. Accordingly, blockade of TGFβ or PDGF signaling has been shown to reduce the development of fibrosis in various experimental models.[21–23] However, substances that specifically inhibit PDGF pathways are not yet available for clinical use. Similarly, anti-TGFβ antibodies and other strategies for blocking TGFβ signaling are only in the early stages of clinical development and have uncertain efficacy in slowing the development of fibrosis in patients with idiopathic scleroderma.[24]

As GVHD is considered to be immune mediated, standard approaches to cGVHD have, to date, been aimed at immunosuppression. As stated above, imatinib mesylate has been shown to inhibit the TGFβ and PDGF pathways.[12,15,16] Furthermore, Distler *et al*. have reported that imatinib mesylate reduces the production of extracellular matrix and prevents the development of experimental fibrosis.[25]

Hence, it is noteworthy that the immunomodulatory effects of imatinib mesylate are now being recognized.[26–28] We do not know whether this drug works predominantly as an immunosuppressant in this setting, as our second patient was already failing to respond to immunosuppressive therapy when imatinib mesylate was added. Likewise, we do not know whether the immune process is linked to the resolution of fibrosis. Nevertheless, it seems reasonable to administer a therapy with a unique mechanism of action to patients who have significant sclerodermatous involvement, where imatinib mesylate's probable effects on fibroblasts make it an attractive approach. Furthermore, it has been reported that the drug has an antifibrotic effect in bleomycin-induced pulmonary fibrosis in rodents.[13,14]

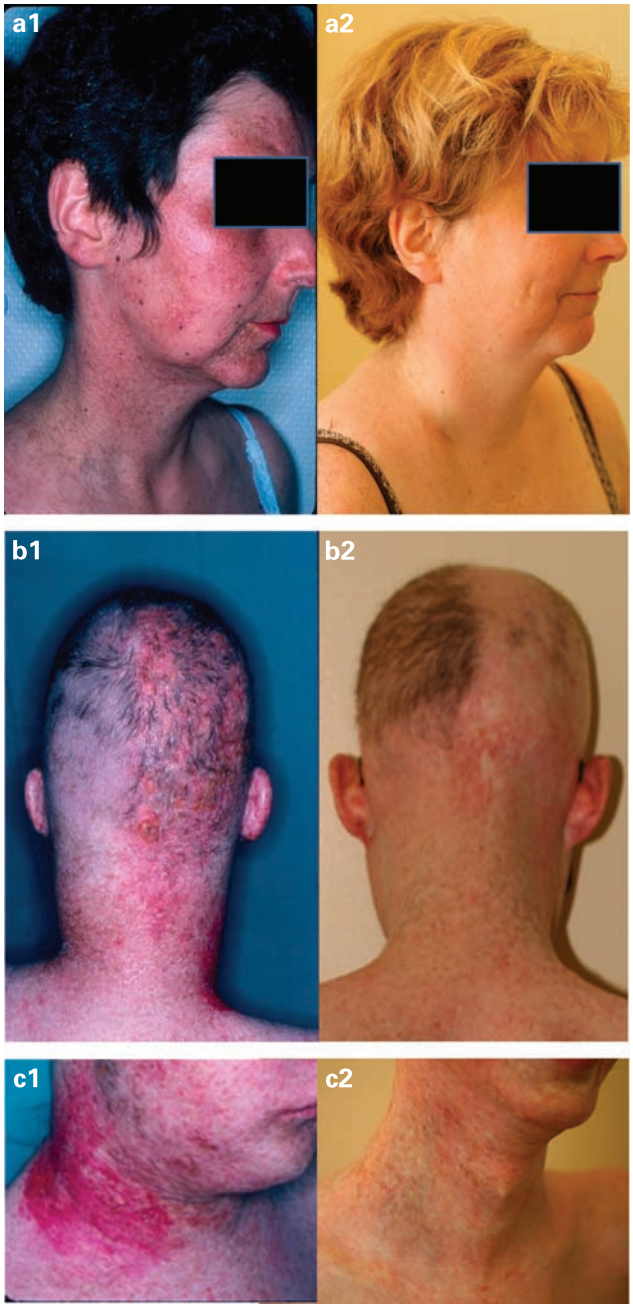

Figure 1 Patient 1, before initiation of imatinib mesylate (**a**1) and how she looks at present (**a**2). Patient 2, before initiation of imatinib mesylate (**b**1 and **c**1) and after 3 months (**b**2 and **c**2).

We believe that these preliminary results are encouraging and warrant further evaluation of imatinib mesylate in the treatment of sclerodermatous cGVHD. Imatinib mesylate may offer a new therapeutic option in this setting but it remains to be seen how the drug could fit into current treatment schemes.

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