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Development of severe sclerotic chronic GVHD during treatment with dasatinib

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In the recently published letter to the editor, Breccia *et al.*[1] described a Philadelphia chromosome positive (Ph +) CML patient who relapsed after haploidentical BMT, and in whom low-dose dasatinib restored the molecular response and improved hepatic chronic GVHD (cGVHD). Moreover, several other recent papers described patients with various fibrotic/sclerotic cGVHD manifestations benefiting from imatinib.[2–4] Stadler *et al.*[5] proposed that stronger effects in cGVHD-induced fibrosis might be possible with the newer tyrosine kinase inhibitors (TKIs).

Dasatinib is a second-generation multitarget TKI approved for treatment of Ph + CML adult patients who are resistant or intolerant to imatinib.[6] Dasatinib is 325-fold more potent than imatinib against unmutated bcr-abl, but also inhibits platelet-derived growth factor receptor, c-Kit, the Src family of kinases, binds to other tyrosine and serine/threonine kinases[6,7] and may have significant antifibrotic potential,[7] which would be of interest when developing new therapeutics for cGVHD. c-Abl and Src kinases are important regulators of extracellular matrix synthesis,[7] and inhibition of Src signaling prevented experimental dermal fibrosis.[8] c-Abl has also recently been implicated in TGF-β-associated fibrosis,[7,9] and blockade of TGF-β or PDGF reduces fibrosis in experimental mod-els.[3,4,7–9] Dasatinib's ability to target T-cell signaling and enhance the inhibitory effect of cyclosporine suggests an additional rationale for its use in cGVHD treatment.[10]

We describe the case of a 22-year-old Latin American man who developed *de novo* severe sclerotic cGVHD after 10/10 HLA matched unrelated donor peripheral blood hematopoietic SCT (HSCT), in spite of continuous treatment with dasatinib after HSCT for the presence of CML. He was diagnosed with Ph + CML in 2005, which was resistant to standard and high-dose imatinib. The patient developed accelerated phase CML and received reducedintensity conditioning HSCT in January 2008. Because of the persistence of residual CML, dasatinib

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Conflict of interest

The authors declare no conflict of interest.

was started on day + 28 post-transplant (range 50–100 mg/day, depending on blood counts). He received sirolimus and tacrolimus for GVHD prophylaxis, which was discontinued on day + 180 without evidence of GVHD. On day + 252 he developed a morbilliform rash on the torso and extremities, and skin biopsy showed lichenoid dermatitis. In November 2008 he developed pure red cell aplasia, and was treated with 4 doses of rituximab 375 mg/m^2 and 4 weeks of i.v. Ig. Beginning in December 2008, while still receiving dasatinib, he developed progressive stiffness of the arms and abdomen. By July 2009, on day +535, he manifested features of sclerotic cGVHD, fascial subtype, with markedly impaired joint range of motion, although a superficial punch skin biopsy of the right arm was not diagnostic for GVHD. At this time, he was started on prednisone 1mg/kg/day, cyclosporine, and occupational and physical therapy. Peripheral blood chimerism revealed 100% donor cells and FISH of BM showed 3% residual CML, and he was continued on dasatinib. In August 2009, magnetic resonance imaging of the right distal humerus revealed subcutaneous edema and probable mild deep fasciitis without definite fascial thickening. He also had slight decline of FEV1 (from 91% pre-transplant to 79%), although asymptomatic, and developed mild oral cGVHD. His range of motion and joint stiffness has improved since starting immunosuppression, and occupational and physical therapy, and he is currently undergoing tapering of prednisone.

cGVHD is a complex clinical syndrome likely encompassing entities of diverse immunobiologies. The case presented here emphasizes the complicated mechanisms underlying soft tissue fibrosis in cGVHD, and our limited understanding of how TKIs exert their effects in this disease. Although we believe that TKIs offer an exciting new avenue for cGVHD management, many questions remain regarding their mechanism of action, appropriate patient selection, dose and duration of therapy.

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