To the editor:

Limited efficacy and tolerance of imatinib mesylate in steroid-refractory sclerodermatous chronic GVHD

Imatinib mesylate (IM), a tyrosine kinase inhibitor, has shown efficacy for the treatment of chronic GVHD (cGVHD),[1-3] with overall response rates of fibrotic skin symptoms evaluated in 2 open-label studies ranging from 50%[1] to 79%.[2] To assess the global long-term effectiveness of IM for sclerodermatous cGVHD, we performed a retrospective study on 39 patients with steroid-resistant disease followed in 6 French hospitals (Table 1). At the onset of IM, all patients had sclerodermatous grade 2 (n = 6, 15%) or grade 3 cGVHD (ie, deep sclerotic features, fasciitis, skin ulcers, or involvement of more than 50% of the body surface area; n = 33, 85%) according to the National Institutes of Health (NIH) grading.[4] Twenty-five patients (64%) had 1 or more organs involved apart from the skin, and bronchiolitis obliterans was observed in 18 patients (46%). Thirty-seven patients (95%) had received 2 or more treatment lines for cGVHD before IM treatment. IM was started after a mean delay of 29 ± 28 months after the diagnosis of cGVHD. The response assessment was made by the physician according to his or her perception of the change in skin involvement evaluated as "improvement," "stability," or "worsening." The physician's perception of skin change was closely related to the NIH composite score that is correlated with overall mortality and was therefore used in this study.[5] After an average treatment duration of 13 ± 10 months, IM did not improve skin sclerosis in 70% of patients (stability = 31%, worsening = 39%). The overall improvement rate was 30%: 1 patient (2%) achieved complete remission (with 28 months of follow-up after IM start), 9 (23%) had improvement, and 2 (5%) had improvement and secondary worsening after initial remission (20 and 22 months after IM start, respectively). Systemic corticosteroids were tapered in 9 patients (23%) and discontinued in 7 patients (18%); however, among these 16 patients, 7 had no improvement of the skin symptoms, so corticosteroid tapering did not reflect the efficacy of IM, but rather the physician's conviction that corticosteroids were ineffective. After a mean follow-up time of 18 ± 12 months after

Table 1. Patient characteristics, GVHD features, and response to imatinib (N = 39)

	Values
Sex ratio, male/female, n	31/8
Mean age, y (range)	42 (5-70)
Diagnosis, n	
AML/ALL	10/8
MM/CML	7/4
Other MPS/MDS	3/2
HD/NHL	2/3
Type of transplantation, sibling/MUD, n	23/16
Stem cell source, PBSC/BM, n	32/7
Conditioning, MA/NMA/RIC, n	27/1/11
GVHD prophylaxis, n	
MTX + CsA/MMF + CsA/CsA	27/11/1
Acute GVHD target organs, n	
Skin/gut/both/none	26/5/6/2
cGVHD target sites, n (%)	
Skin (fibrotic features)	39 (100)
Eye and/or mouth mucosa	32 (82)
Lung (bronchiolitis obliterans)	18 (46)
Liver	9 (23)
Digestive tract	6 (15)
2 or more target sites	25 (64)
cGVHD skin scoring, n (%)	
Grade 3 (> 50% BSA OR deep sclerotic features OR ulcerations OR inability to move)	33 (85)
Grade 2 (< 50% BSA and/or superficial sclerotic features only)	6 (15)
Previous treatments for cGVHD, n (%)	
Systemic corticosteroids	39 (100)
MMF	30 (77)
CsA	24 (62)
ECP	14 (36)
RTX/rapamycin/evero/thali/MTX/AZA/pento	7/6/2/2/1/1/1
PUVA/TAI/TLI	4/3/1
2 or more previous treatments for cGVHD	37 (95)
Mean time from cGVHD to imatinib start, mo (SD)	29 (28)
Imatinib maximal daily posology, mg, n	
100/200/300/400/600	9/8/9/13/1
Mean IM treatment duration, mo (SD)	**13 (10)**
Concomitant treatments for cGVHD, n (%)	
Systemic corticosteroids	33 (85)
MMF	15 (38)
CsA	12 (31)
ECP	6 (15)
Rapamycin	3 (8)
2 or more concomitant treatments	25 (64)
Physician global assessment of skin cGVHD evolution after imatinib start, n (%)*	
Complete remission	1 (2)
Improvement	9 (23)
Improvement, then relapse	2 (5)
Stability	12 (31)
Worsening	15 (39)
Overall improvement of skin cGVHD after IM start, n (%)	12 (31)
Corticosteroids tapered, n (%)	9 (23)
Improvement of skin cGVHD, n	3
Stability of skin cGVHD, n	5
Worsening of skin cGVHD, n	1
Corticosteroids discontinued, n (%)	7 (18)
Improvement of skin cGVHD, n	6
Stability of skin cGVHD, n	1
Grade 3 or 4 adverse events (WHO), n (%)	12 (31)
Cytopenias	3 (8)
Generalized fluid retention	7 (18)
Impaired consciousness	2 (5)
Outcome at the last follow-up, dead/alive, n	6/33
Mean follow-up after imatinib start, mo (SD)	**18 (12)**

ALL indicates acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; AZA, azathioprin; BSA, body surface area; CML, chronic myelogenous leukemia; CsA, cyclosporin A; ECP, extracorporeal photopheresis; evero, everolimus; HD, Hodgkin disease; MA, myeloablative conditioning; MDS, myelodysplastic syndrome; MM, multiple myeloma; MMF, mycophenolate mofetil; MPS, myeloproliferative syndrome; MTX, methotrexate; MUD, matched unrelated donor; NHL, non-Hodgkin lymphoma; NMA, nonmyeloablative conditioning; PBSCs, peripheral blood stem cells; pento, pentostatin; PUVA, psoralen + UVA therapy; RIC, reduced-intensity conditioning; RTX, rituximab; Sib, sibling; tacro, tacrolimus; TAI, thoracoabominal irradiation; thali, thalidomide; TLI, total lymphoid irradiation; and WHO, World Health Organization.

*At the time of imatinib discontinuation or at the last follow-up if imatinib treatment was not discontinued.

IM start, IM had been discontinued in 22 patients (56%). Serious adverse events included mainly generalized fluid retention (n = 7, 18%) and cytopenias (n = 3, 8%) that required discontinuation of the drug.

We conclude that IM has limited efficacy and tolerance in the setting of severe sclerodermatous cGVHD. These poorer outcomes compared with the 2 previous studies may be explained by at least 3 factors: (1) our patients had more severe sclerodermatous cGVHD, (2) our patients were older, and (3) our study included the largest number of patients with the longest follow-up times. Stimulatory Abs to anti-PDGFR (a tyrosine kinase receptor) were found in extensive cGVHD,[6] but the lack of correlation between response to IM and these Abs[3] suggests that the mechanism of IM activity in cGVHD and the pathophysiology of cGVHD itself are far from being fully elucidated. The characteristics of the few patients who may benefit from IM treatment remain to be determined in future prospective studies.

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Contribution: A.D.M., J.-D.B., and R.P.d.L. analyzed the results; A.D.M. and J.-D.B. wrote the manuscript; S.W., P.R., M.-T.R., J.-B.M., F.S., S.N., J.-H.D., K.Y., M. Robin, A.X., L.A., J.-H.B., and M. Rybojad provided patient care and helped collect the data; and J.-D.B., M. Rybojad, M.B., and G.S. reviewed the manuscript and supervised the study.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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