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ORIGINAL ARTICLE

Sclerodermatous Chronic Graft-versus-Host Disease Treated With Imatinib: A Dermatological Perspective☆

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Abstract
Introduction: Chronic graft-versus-host disease (cGVHD) is the most important cause of late non-relapse mortality after allogeneic hematopoietic stem cell transplantation. Sclerodermatous cGVHD is usually steroid refractory and remains a therapeutic challenge. Activating antibodies against the PDGFR have been reported in patients with sclerodermatous cGVHD. These antibodies induce PDGFR phosphorylation and lead to fibrosis. There is increasing evidence of successful treatment of sclerodermatous cGVHD with imatinib, a tyrosine kinase inhibitor.
Objective: To evaluate the response of cutaneous sclerodermatous cGVHD to imatinib.
Materials and methods: Retrospective study of 18 patients with sclerodermatous cGVHD refractory to immunosuppressants treated with imatinib in a single center. Evaluation of treatment response was performed by clinicians' assessment and patients' subjective response at one, 3, 6, 9, 12 and 18 months after initiation of imatinib. Response was assessed as complete, partial, significant, no change or progression. Tapper off steroids was complete, partial or not possible.
Results: In our series, 4 (22%) patients achieved complete response, 9 (50%) patients partial response, 2 (11%) patients significant response, 2 (11%) patients had no change and one (6%) patient progressive disease at last follow-up. Mean time from initiation of imatinib to any degree of response was 2,75 months (range 1-9 months).
Conclusions: This study provides further evidence of the role of imatinib for the treatment of steroid refractory sclerodermatous cGVHD.

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Tratamiento de la enfermedad de injerto contra huésped crónica esclerodermiforme con imatinib: una perspectiva dermatológica

Resumen

Introducción: La enfermedad de injerto contra huésped crónica (EICHc) es la causa más importante de mortalidad tardía no relacionada con la recidiva del trasplante alogénico de células progenitoras hematopoyéticas. La EICHc esclerodermiforme suele ser refractaria a los corticosteroides y supone todo un reto terapéutico. Se han descrito anticuerpos activadores contra el RFCDP en pacientes con EICHc esclerodermiforme. Estos anticuerpos inducen la fosforilación del RFCDP, produciendo fibrosis. Hay cada vez más evidencias de la efectividad de imatinib, un inhibidor de la tirosina cinasa, en el tratamiento de la EICHc esclerodermiforme.

Objetivo: Evaluar la respuesta de la EICHc esclerodermiforme al imatinib.

Materiales y métodos: Estudio retrospectivo de 18 pacientes con EICHc cutánea esclerodermiforme refractaria a inmunosupresores tratada con imatinib en un único centro. La evaluación de la respuesta al tratamiento se realizó mediante valoración clínica del dermatólogo y percepción subjetiva del paciente tras uno, 3, 6, 9, 12 y 18 meses de iniciar el tratamiento con imatinib. La respuesta fue valorada como completa, parcial, significativa, sin cambios o progresión. El descenso de la dosis de esteroides se catalogó como completo, parcial o no posible.

Resultados: En nuestra serie, 4 (22%) pacientes lograron una respuesta completa, 9 (50%) alcanzaron una respuesta parcial, 2 (11%) tuvieron un grado significativo de respuesta, 2 (11%) no presentaron ningún cambio y uno (6%) experimentó avance de la enfermedad en el último seguimiento que se llevó a cabo. El tiempo medio transcurrido desde el inicio del imatinib hasta mostrar algún grado de respuesta fue de 2,75 meses (rango 1-9 meses).

Conclusiones: Este estudio apoya la evidencia de la utilidad del imatinib en el tratamiento de la EICHc esclerodermiforme.

Allogeneic hematopoietic stem cell transplant (HSCT) is the only curative treatment for several diseases. The increasing use of this procedure, including more unrelated donors, older patients, the use of peripheral blood, and less treatment related mortality have raised the prevalence of chronic graft-versus-host disease (cGVHD).[1] Chronic GVHD accounts for 20-40% of deaths[2–4] and it is a major determinant in the survival and quality of life of patients after HSCT, not only due to the symptoms, but also resulting from the complications of long-term immunosuppression.[5]

Chronic GVHD results from auto, alloimmune and immunodeficiency processes. Alloreactivity is induced by histocompatibility complex incompatibilities between donor and recipient. It often mimics autoimmune diseases, with loss of immune tolerance by impaired thymic negative selection that allows expansion and activation of autoreactive T and B cells.[6]

Sclerodermatous GVHD is a rare and severe form of cGVHD that accounts for 10-15% of cases[7] frequently refractory to treatment with steroids and other immunosuppressants. Activating antibodies against the PDGFR[8] have been described in patients with sclerodermatous cGVHD. These antibodies trigger an intracellular loop, involving a-Ras-extracellular-signal-regulated kinases 1 and 2 - reactive oxygen species, which leads to increased type 1 collagen expression and myofibroblast phenotype conversion of normal fibroblasts.[4] Likewise, other pro-fibrotic cytokines, such as TGF-β have been identified and anti-TGF-β antibodies prevented the development of skin fibrosis in a murine model.[9]

Imatinib mesylate (IM) (Glivec and Gleevec; Novartis, Basel, Switzerland) is a potent inhibitor of the tyrosine kinases BCR-ABL, PDGFR α and β, c-KIT and ABL, among others, that has proven effective for treatment of malignancies that harbor a constitutive activation of these kinases. Recent studies have shown that IM also strongly inhibits TGF-β.[10] In view that IM is a dual inhibitor of the PDGFR and TGF-β pathways, it has been used in patients with fibrotic features with most cases presenting complete or partial response.[11] We describe the outcome of 15 patients treated with IM for refractory sclerodermatous cGVHD.

Materials and methods

Patient selection

A retrospective study was conducted in a single allo-SCT center. All patients with cutaneous sclerodermatous cGVHD treated with IM and referred to the Dermatology department between 2001 and 2016 were included.

Data collection

Data were collected from electronic charts. Demographic data, past medical history and type of transplant

Table 1 Patient and transplantation characteristics.

	Sex	Age (y)	Condition	Conditioning	Type	Cell source	GVHD profilaxis	aGVHD sites (grade)	cGVHD sites	Immunosuppression before imatinib
1	M	63	AML	MAC	HLA id	PBSC	CS-TAC	No	Skin, intestine, lung, joint contracture	MMF
2	M	24	AML	MAC	HLA id	BM	CSA-MTX	Skin (1), liver (3)	Skin, mouth, liver	CS, MMF, PT
3	F	23	CML	MAC	NRD	UCSC	CS-CSA	No	Skin, intestine, lung	MMF, CS
4	M	43	AML	MAC	HLA id	PBSC	CS-CSA	Skin (3)	Skin, mouth, eyes	TAC, CS, PT, ETN
5	F	35	CLL	RIC	HLA id	PBSC	CSA-MMF	No	Skin, mouth, eyes, liver	CS
6	F	37	ALL	MAC	HLA id	PBSC	CSA-MTX	No	Skin, eyes, liver, joint contracture	CS
7	F	54	AML	MAC	HLA id	PBSC	CSA-MTX	No	Skin, mouth, eyes, liver	CS, CSA
8	M	34	AA	MAC	HLA id	PBSC	CSA-MTX	No	Skin, mouth, eyes, lung	TAC, CS, PT
9	F	27	AML	MAC	HLA id	PBSC	CSA-MTX	No	Skin, mouth, eyes, liver, lung	CS
10	F	31	AML	MAC	HLA id	PBSC	CSA-MTX	Skin (1)	Skin, mouth, eyes, intestine, liver, lung,	MMF
11	M	48	AML	MAC	NRD	UCSC	CS-CSA	Skin (1)	Skin, eyes, intestine, lung	CS
12	M	52	CLL	RIC	HLA id	PBSC	CSA-MTX	Skin (2)	Skin, mouth, eyes, intestine	CS, CSA, ATG, MMF
13	M	46	NHL	RIC	HLA id	PBSC	CSA-MTX	Skin (2)	Skin, nails, eyes	CS
14	M	13	ALL	MAC	Haplo	PBSC	CY-MMF-TAC	Skin (3)	Skin, mouth, eyes, liver	No
15	F	30	AML	MAC	HLA id	PBSC	CSA-MTX	Liver (1), intestine (1)	Skin, mouth, liver	CS, PT
16	F	50	AML	MAC	HLA id	PBSC	CSA-MTX	No	Skin, eyes	No
17	F	55	AML	IR	HLA id	PBSC	CSA-MTX	No	Skin, liver, hematopoyetic	CS, TAC
18	M	43	ALL	MAC	HLA id	PBSC	CSA-MTX	Skin (2) GI	Skin, intestine	No

M: male, F: female, Y: years, AML: acute myeloid leukemia, CML: chronic myeloid leukemia, CLL: chronic lymphocytic leukemia, ALL: acute lymphoblastic leukemia, AA: aplastic anemia, NHL: non-Hodgkin lymphoma, MAC: myeloablative conditioning, RIC: reduced intensity conditioning, NE: not evaluable, HLA id: HLA identical, Haplo: HLA haploidentical, NRD: non-related donor, PBSC: peripheral blood stem source, BM: bone marrow, UCSC: umbilical cord stem cell, CS: corticosteroids, CSA: cyclosporine A, MMF: Mycofenolate mofetil, MTX: methotrexate, CY: cyclophosphamide, TAC: tacrolimus, PT: phototherapy, ETN: etanercept, ATG: antitimoglobuline.

Table 2 Organs affected by chronic GVHD.

Skin	18
Eyes	12
Liver	9
Mouth	8
Gastrointestinal tract	6
Lung	5
Musculoskeletal system	2
Nails	1
Hematopoietic system	1

were recorded including conditioning regimen and GVHD prophylaxis.

Response criteria

Evaluation of treatment response was performed by clinicians' assessment and patients' subjective response at 1, 3, 6, 9, 12 and 18 months after initiation of IM. Clinical response was assessed as: ''complete response'', ''partial response'', ''significant response'', ''no change'', or ''progression''. Complete response was defined as resolution of all manifestations, partial response as an improvement of more than 50% without any new organ involvement or progression in a previously involved organ, and significant response as less than 50% improvement. No change was defined as the absence of improvement. Steroid dose tapper off was evaluated as ''complete'', ''partial'', or ''not possible''. Treatment duration was at the discretion of the physician.

Results

Patient characteristics

In total 18 patients were included (10 male and 8 female). Patient and transplant characteristics are summarized in Table 1. Acute myeloid leukemia was the most frequent preceding diagnosis. Median age at time of HSCT was 39 years (range 13-63). Fifteen (83%) transplants were HLA-identic sibling. All patients received GVHD prophylaxis, in which cyclosporine plus short course methotrexate was the most common regimen. Nine (50%) patients had history of acute GVHD. The mean number of affected organs by cGVHD was 3.5. Skin, eyes and liver were the most frequently involved (Table 2).

Patients received an average of 1.6 immunosuppressants before IM. The overall median follow-up until treatment suspension because of no further improvement or treatment failure was 27 months (range 1-89 months). Only patient No. 6 received IM intermittently, the remaining were on the drug continuously. IM dose was between 100-300 mg daily (in two doses).

Treatment response

Mean time from initiation of IM to any degree of response was 2,75 months (range 1-9 months). After 1 month, 10 (66.7%) patients had partial or significant response but none achieved a complete response and 6 (33.3%) showed no changes. Of the 13 (86.7%) patients evaluated at 6 months, only 1 (7.7%) patient had a complete response, 5 (38.5%) had partial or significant response, 6 (46%) patients had no change, and in 1 (7.7%) patient the symptoms progressed. Ten (55.6%) patients were assessed at 12 months, with 1 (10%) complete response, 7 (70%) significant or partial response, 1 (10%) no change and 1 (10%) progression. Only 8 (44.4%) patients achieved 18 months follow up, 3 (37.5%) with a complete response, 4 (50%) with partial response and 1 patient (12.5%) showed no change.

Overall, 4 (22%) patients achieved complete response, 9 (50%) patients partial response, 2 (11%) patients significant response, 2 (11%) patients had no change and 1 (6%) patient showed progressive disease at last follow-up. A complete suspension of steroids was achieved in 4 (22%) patients, partial reduction in 10 (55.6%) patients and no dose reduction was possible in 4 (22%) patients.

It is noteworthy that patients with early response to IM maintained it through all follow up, and those without response in the first months did not show improvement later. Only patient No. 12 had initially a partial response but progression at 12 months follow up.

Seven (39%) patients presented adverse reactions consisting of cramps, headache, hypophosphatemia, edema and thrombocytopenia. There were no withdrawals due to adverse effects. All patients (93.3%) except No. 12 are alive and 11 (61%) remain indefinitely on IM (Table 3).

Discussion

Sclerodermatous cGVHD is characterized by chronic inflammation and fibrosis of the skin, lung and gastrointestinal tract that resembles systemic sclerosis. Topical and systemic steroids are the standard treatment. However, second line therapy is required in 50% of cases, such as cyclosporine, tacrolimus, mycophenolate mofetil, methotrexate, sirolimus, phototherapy and extracorporeal photopheresis.[12] These treatments are limited by their adverse effects and have not showed improvement in the long-term outcome. Therefore, no current therapies used for cGVHD are approved by the Food and Drug Administration therefore it is recommended that refractory cGVHD should be treated under experimental protocols.[11]

This study shows that IM is effective in sclerodermatous cGVHD even at low doses. In our series, 15 of 18 (83%) patients achieved complete, partial or significant response, 2 (11%) had no change and 1 (6%) experimented progressive disease at last follow-up. Our results are similar to the study by Olivieri et al, in which 19 patients were treated with IM for refractory cGVHD with fibrotic features. IM dose

Table 3 Response at 1, 3, 6, 9, 12 and 18 months after start of imatinib.

Case no.	Maximal tolerated daily dose of IM (mg)	IM therapy duration at last follow-up (mo)	Side effects	IM discontinuation at last follow-up	cGVHD status at 1 mo of IM	cGVHD status at 3 mo of IM	cGVHD status at 6 mo of IM	cGVHD status at 9 mo of IM	cGVHD status at 12 mo of IM	cGVHD status at 18 mo of IM	Tapper off CS	Patient status
1	200	10	No	Yes	NC	NC	NC	SR	Treatment suspended		Partial	Alive
2	100	2	No	Yes	SR	Treatment suspended					Complete	Alive
3	200	5	No	Yes	PR	PR	Treatment suspended				Partial	Alive
4	200	32	Hypophosphatemia	No	NC	NC	NC	SR	PR	PR	Partial	Alive
5	200	6	Cramps	Yes	SR	NC	NC	PR	Not achieved	Not achieved	Partial	Alive
6	200	24	Cramps, headache	No	PR	PR	PR	PR	PR	PR	Partial	Alive
7	200	48	Edema	No	PR	PR	PR	PR	PR	CR	Complete	Alive
8	200	1	No	Yes	PR	Treatment suspended					No	Alive
9	200	15	No	No	NC	SR	SR	SR	NC	CR	Partial	Alive
10	200	1	No	Yes	NC	NC	Treatment suspended				No	Alive
11	200	14	No	No	SR	CR	CR	CR	CR	Not achieved	Partial	Alive
12	200	21	No	No	PR	PR	Prog	NC	Prog	NC	No	Dead
13	200	16	Cramps	Yes	NC	SR	PR	PR	PR	Not achieved	No	Alive
14	300	1	Trombocitopenia	Yes	PR	Treatment suspended					Partial	Alive
15	200	5	No	No	NC	NC	NC	Treatment suspended			Partial	Alive
16	200	84	Cramps	No	SR	SR	SR	SR	SR	PR	Complete	Alive
17	100	58	No	No	SR	SR	NC	SR	SR	PR	Complete	Alive
18	200	89	No	No	SR	SG	NC	NC	PR	CR	Partial	Alive

Mo: months, IM: imatinib, NC: no change, PR: partial response, SR: significant response, CR: complete response, Prog: progression.

was 100-400 mg/day. Fifteen patients (79%) responded at 6 months, and overall survival rate was 84% at 18 months.[11] Subsequently, Magro et al reported an overall response of 50% in a retrospective study of 14 patients with refractory sclerotic cGVHD.[13] In contrast, de Masson et al. reported limited efficacy and tolerance of IM in the setting of severe sclerodermatous cGVHD in 39 patients. They attributed the poorer outcomes to patients' older age, more severe disease and longest follow-up period.[14]

It has been reported that about 10% of patients do not tolerate IM.[15] Its most common side effects reported in series of cGVHD are fluid retention and cytopenias. In our study, IM was reasonably well tolerated by almost all patients. However, the doses used were lower than that of CML (400 mg/day).

Another benefit of treatment with IM is the reduction in steroids dose, which was possible in 14 (77.8%) of patients to some degree. Hitherto, it is not known if the immune process is linked to the resolution of fibrosis neither if IM may be useful in the absence of sclerotic features. Additionally, it is not possible to discriminate patients who will benefit from those who will not improve.

Two other more potent kinase and PDGFR inhibitors (dasatinib and nilotinib) are in the early stages of investigation.[16] Besides the PDGFR pathways, EGFR is also implicated in fibrotic diseases. In this context, erlotinib is a potent EGFR tyrosine kinase inhibitor used to treat advanced non-small-cell lung cancer, and has recently been tested to prevent skin and visceral sclerodermatous lesions in a mouse model of cGVHD.[7]

In summary, IM represents a valuable option for patients with sclerodermatous cGVHD, it is a simple treatment that requires neither hospitalization nor central venous access with an acceptable safety profile. Nonetheless, IM is not effective in all patients with cGVHD, and the response is often partial. Further evidence from well-controlled randomized multicenter prospective trials using the National Institute of Health Consensus Response Criteria is needed to confirm the true efficacy of IM.

The limitations of this study are the reduced number of patients and the retrospective design. Cutaneous sclerosis and treatment response were subjectively assessed, and grading of IM toxicity was not recorded in patients' charts.

As there is greater understanding of the pathophysiology treatment for cGVHD will rapidly develop. Novel strategies such as therapies that target B lymphocytes, expand regulatory cells and target the fibrotic process are under investigation.[17] In the future, we may be able to provide tailored therapies for individual patients and separate the graft versus tumor effect from the debilitating symptoms of this disease.[18]

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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