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The Experience of Ibrutinib in Chronic Graft-Versus-Host Disease in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation: Single Center Experience

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ABSTRACT

Introduction: Chronic graft-versus host disease (GVHD) is a serious complication that develops in 35-50% of patients in the late period after allogeneic hematopoetic stem cell transplantation. About half of the patients are resistant to corticosteroids, which is the first-line treatment of chronic GVHD, and therefore new treatment options that can be effective in chronic GVHD are needed. In the present study, we aimed to share our experience with the use of ibrutinib therapy in patients with steroid-resistant chronic GVHD who have previously received multiple lines of systemic therapy.

Methods: The characteristics and clinical outcomes of steroid-resistant chronic patients with GVHD receiving ibrutinib were retrospectively reviewed.

Results: A total of 10 steroid resi-stant chronic patients with GVHD who received ibrutinib was included. While 50% of the patients had more than one organ involvement, 50% had a single organ involvement. The most commonly affected organs were the skin and liver. The patients received a median of three lines of systemic therapy before ibrutinib. After a median of 210 days of ibrutinib usage, the complete response rate of patients was 40% and the partial response rate was 40%. Corticosteroids were completely discontinued in 30% of patients after ibrutinib were initiated. Before ibrutinib, patients were given a median of 0.3 mg/kg methylprednisolone. The median methylprednisolone dose after ibrutinib was 0.03 mg/kg.

Conclusion: Ibrutinib therapy causes a quite high overall response in steroid resistant chronic patients with GVHD and appears to be a good option in these patients.

Keywords: Steroid-resistant graft-versus host disease, ibrutinib, corticosteroids, allo-HSCT, chronic GVHD

Introduction

Allogeneic hematopoetic stem cell transplantation (allo-HSCT) is a curative treatment option for many hematological diseases such as acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome, aplastic anemia and paroxysmal nocturnal hemoglobinuria. However, early (<3 months) and late (>3 months) complications that cause transplant-related morbidity and mortality are observed in many patients after allo-HSCT.

Early complications of allo-HSCT include graft-versus host disease (GVHD), bacterial, viral and fungal infections, engraftment syndrome, hemorrhagic cystitis, capillary leak syndrome, graft failure, hepatic sinusoidal obstruction syndrome, pulmonary complications and transplant-related thrombotic microangiopathy (1,2). The mortality rate due to early complications varies between 5% and 40%, depending on factors such as transplantation from donor, pre-transplant regimen, age, and comorbidities of the patient (3).

Late complications following allo-HSCT include chronic GVHD, idiopathic pneumonia, bronchiolitis obliterans, pulmonary and nonpulmonary infections, hypogonadism, osteopenia, hypertension, hypothyroidism, dyslipidemia, diabetes mellitus, chronic kidney disease, cardiomyopathy,

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heart failure, and secondary malignancies (4). Although allo-HSCT is a curative option for treating many hematological diseases, life expectancy after allo-HSCT is still lower (5,6). The most common causes of mortality in the late period following allo-HSCT are recurrence of primary malignancy, chronic GVHD, infections, secondary malignancies, pulmonary complications, and cardiac toxicity, respectively (6).

Chronic GVHD is a severe difficulty that improves in 35-50% of patients in the late period after allo-HSCT and is the second most common cause of mortality in patients with allo-HSCT (6,7). In patients with chronic GVHD, the most commonly involved organ is the skin, but other organs such as the mouth, eyes, liver, gastrointestinal system, lungs, joints, fascia, genital organs, and hematopoietic system can also be involved (8,9). In recent years, with the increasing number of patients with allo-HSCT, the number of patients with chronic GVHD has also increased. Approximately half of the patients are resistant to corticosteroids, which are the first choice for treating chronic GVHD; thus, new treatment options that can be effective in chronic GVHD are needed.

The guidelines recommend that patients should participate in well-designed clinical trials because there is no standard second-line treatment for chronic GVHD (10,11). In the absence of a clinical trial option, guidelines recommend the administration of one of the following agents: ibrutinib, ruxolitinib, abatacept, imatinib, calcineurin inhibitors, alemtuzumab, extracorporeal photopheresis, hydroxychloroquine, low-dose methotrexate, mTOR inhibitors, bortezomib, mycophenolate mofetil, pentostatin, rituximab. Ibrutinib has been approved by the US Food and Drug Administration for the treatment of chronic GVHD patients who are resistant to one or more lines of systemic therapy.

Due to the uncertainty of optimal therapy in corticosteroids resistant chronic GVHD patients, we aimed to present our experience in chronic GVHD patients who have previously received multiple lines of systemic therapy

Methods

Patients who developed chronic GVHD between February 2011-2021 and who were started on ibrutinib after at least two lines of treatment were included in the study. After the study was approved by the İnönü University Ethics Committee (decision no: 2022/2946), demographic, clinical, and laboratory data of the patients were retrospectively analyzed using the hospital electronic information system. Written informed consent was obtained from the patients included in the study.

Within the framework of the criteria recommended by the National Institutes of Health (NIH), chronic GVHD was defined as a complication occurring at any time after allo-HSCT and differentiated from acute GVHD with its clinical features (12). Chronic GVHD severity was defined as mild, moderate, and severe within the framework of the criteria recommended by the NIH (13). While systemic treatment was initiated with corticosteroids in patients with moderate to severe chronic GVHD, it was not preferred in patients with mild chronic GVHD.

Ibrutinib was initiated at a dose of 420 mg per day and continued at this dose until grade 3 or 4 toxicity occurred. We reduced the ibrutinib dose to 140 mg in patients who were given posaconazole as antifungal prophylaxis.

Ibrutinib-related adverse events were classified according to the Common Toxicity Criteria for Adverse Events version 5.0 (12).

As recommended by the NIH, patients with a resolution of all symptoms in all involved organs were considered to have a complete response to treatment. Patients with improvement in at least one involved organ without progression in other organs were considered to have a partial response to treatment. The overall response rate was considered as the sum of the complete response rate and the partial response rate (12).

Statistical Analysis

IBM SPSS 25.0 was used as the statistics program. Normality analysis of the data was performed using the Shapiro-Wilk test, and the data were given as median, range, and percentage.

Results

A total of 10 patients with steroid-resistant chronic GVHD who received ibrutinib were included in this study. Steroid resistant chronic GVHD

Table 1. Characteristic features of ibrutinib treated chronic GHVD patients

Patient no.	Age	Gender	Disease	Donor	Involved organ(s)	Severity
1	38	Male	AML	MRD	The skin, eye, mouth	Moderate
2	22	Male	AML	MRD	Liver	Moderate
3	22	Male	AML	UMD	Liver	Moderate
4	29	Female	AML	MRD	The liver, skin	Moderate
5	19	Male	AML	MRD	The liver, skin	Moderate
6	21	Male	BTM	MRD	Intestine	Severe
7	60	Male	AML	MRD	Skin	Severe
8	41	Male	AML	MRD	The skin, intestinal, liver	Moderate
9	19	Male	ALL	MRD	Skin, intestine	Moderate
10	19	Male	ALL	MRD	Liver	Moderate

GVHD: Graft-versus-host disease, AML: Acute Myeloid Leukemia, BTM: Beta thalassemia major, MRD: Matched-related donor, UMD: Unrelated-matched donor

developed in seven patients with AML, two with ALL, and one with beta thalassemia major. While 50% of the patients had more than one organ involvement, 50% had a single organ involvement. The most frequently involved ones are skin (60%) and liver (60%) (Table 1). All patients with skin involvement (n=6) had non-sclerotic features. There were no patients with sclerotic involvement.

All patients included in the study received myeloablative regimen before allo-HSCT. In our patients, chronic GVHD was diagnosed a median of 165 (50-500) days after allo-HSCT. Ibrutinib was initiated in a median of 150 (102-660) days after the diagnosis of chronic GVHD. Before ibrutinib, patients had received a median of 3 (2-4) lines of systemic therapy, including corticosteroids, cyclosporine, mycophenolate mofetil, and extracorporeal photopheresis.

Although the median follow-up time for 10 patients was 394 (100-750) days, it was 210 (30- days) under receiving ibrutinib. After a median of 210 days of treatment with ibrutinib, the complete response rate of patients was 40% and the partial response rate was 40% (Table 2).

Median time to onset of a response to ibrutinib in 8 patients was 52 (25-125), and median response duration of patients to ibrutinib was 143 (70-415) days. Organ involvement features of patients are given in Table 3.

After a median follow-up of 394 days, median failure-free survival could not be achieved in both the entire population and those who responded to ibrutinib (Figure 1, 2). No association was found between the severity of GVHD and the ibrutinib response (p=0.378). When those who received ≤3 lines of treatment before ibrutinib and those who did not receive more than 3 lines of treatment were compared, no difference was found between the GVHD response and OS of the two groups (p=1 and p=0.537, respectively).

We observed ibrutinib-related adverse events in two (20%) of 10 patients. In one patient (patient 2) with liver GVHD, ibrutinib was discontinued because of elevated liver enzymes (grade 3 alanine aminotransferase elevation) 30 days after initiation. This adverse event resolved 20 days after ibrutinib was discontinued. In another patient (patient 3), we observed grade 4 thrombocytopenia 50 days after initiation. Ibrutinib was discontinued for 27 days, the adverse event disappeared, and we continued ibrutinib at the same dose.

Corticosteroids were completely discontinued in 30% of patients after ibrutinib were initiated. Before ibrutinib treatment, patients were given a median of 0.3 mg/kg methylprednisolone. The median methylprednisolone dose after ibrutinib was 0.03 mg/kg. The median

Table 2. Clinical outcomes of ibrutinib trea-treatednic patients with GVHD

Patient no.	7-day survival	28-day survival	90-day survival	180-day survival	The partial response (%)	The complete response (%)	No response (%)	GVHD mortality	Non-GVHD mortality
1	+	+	+	+	Yes			No	No
2	+	+	+	+			Yes	No	Yes (relapse)
3	+	+	+	+	Yes			No	No
4	+	+	+	+		Yes		No	No
5	+	+	+	+	Yes			No	No
6	+	+	+	-			Yes	Yes	No
7	+	+	+	+		Yes		No	No
8	+	+	+	+		Yes		No	No
9	+	+	+	+		Yes		No	No
10	+	+	+	+	Yes			No	No
Overall response	100%	100%	100%	90%	40%	40%	20%	10%	10%

Table 3. Organ response of ibrutinib-treated chronic GHVD patients

Patient no.	Involved organ(s)	Response by organ(s)
1	The skin, eye, mouth	Skin
2	Liver	No response
3	Liver	Liver
4	The liver, skin	The liver, skin
5	The liver, skin	Liver
6	Intestine	No response
7	Skin	Skin
8	The skin, intestinal, liver	The skin, intestinal, liver
9	Skin, intestine	Skin, intestine
10	Liver	Liver

GVHD: Graft-versus-host disease

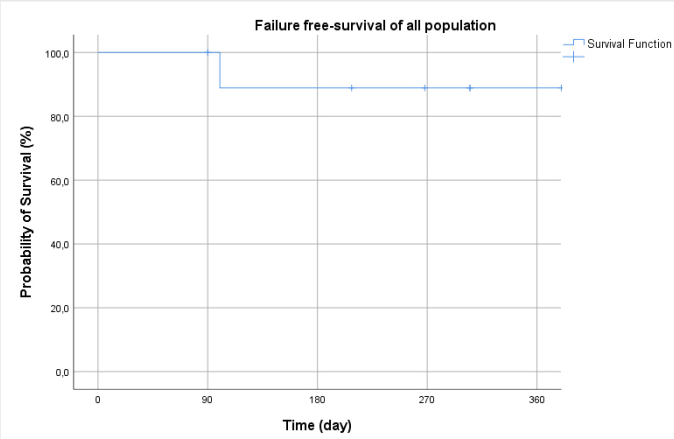

Figure 1. Failure free-survival of all population

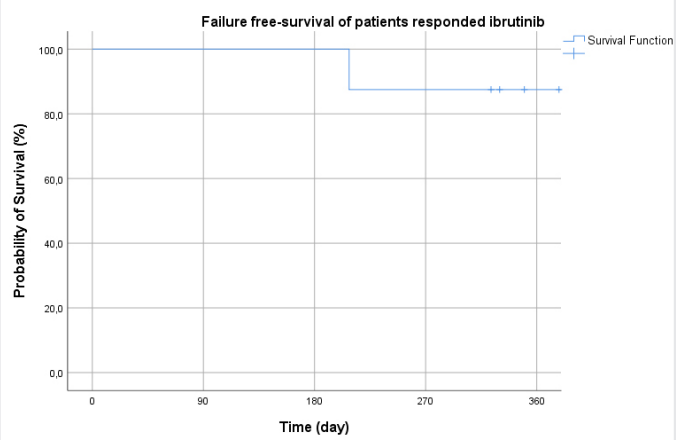

Figure 2. Failure free-survival of patients responded ibrutinib

time to reduce the steroid dose was 43 (15-295) days. In 3 patients, steroid was completely discontinued after a median of 96 (50-115) days.

Discussion

Chronic GVHD is the most important cause of non-relapse mortality and affects quality of life in the late period following allo-HSCT (6,14). The treatment approach is not standard in steroid resistant chronic patients with GVHD because well-designed comparative studies of in these patients are lacking.

In retrospective studies that evaluated the efficacy of mycophenolate mofetil, sirolimus, rituximab, pentostatin, and ruxolitinib in steroid resistant chronic GVHD patients, overall response rates ranged from 55-81% (15-19). In phase 2 studies evaluating the efficacy of imatinib, sirolimus (in combination with tacrolimus), rituximab, and pentostatin in steroid resistant chronic GVHD patients, overall response rates ranged from 27-63% (20-22). Because of the uncertainty of the optimal agent to be chosen in second-line therapy, treatment should be determined according to affected organs (eg. sirolimus for joint, ruxolitinib for skin), patient renal and liver functions, side effects of the agents, patient preferences and clinician's experience (7).

Ibrutinib has been shown to inhibit Bruton's tyrosine kinase and interleukin-2-inducible T-cell kinase, which play an important role in the pathogenesis of chronic GVHD, thereby reducing the activation of T- and B-cells in the murine chronic GVHD model (23). Based on this data, researchers designed a phase 1b/2 study to determine the safety and efficacy of ibrutinib in chronic GVHD patients who received at least 1 line of systemic corticosteroids therapy. Eighty-six percent of patients had mouth, 81% had skin, 36% had gastrointestinal system, 7% had liver, and 5% had a lung involvement. In this study, after the initiation of ibrutinib, a complete response was obtained in 21.4% (9/42) of patients and a partial response was obtained in 45.2% (19/42) of them in addition, 47.6% of patients (20/42) had a sustained response to ibrutinib for 20 weeks or longer (24). In the present study, two-thirds of the patients responded to ibrutinib, whereas the response rate was found to be slightly higher (%80) in our study evaluating fewer chronic GVHD patients.

In a retrospective single-center study in a total of 22 pediatric patients with chronic GVHD, a partial response was achieved in 54.5% of patients with ibrutinib at a dose of 250 mg/m^2. Ibrutinib was reduced by 50% in 16 patients who received voriconazole or posaconazole concomitantly. Of the 12 patients who responded to ibrutinib, the corticosteroids dose was reduced in 9 of them, and corticosteroids were discontinued in 2 of them (25). In our study, corticosteroids were completely discontinued in 3 of 8 patients who responded to ibrutinib, and the corticosteroids were reduced in 3 of them.

In a retrospective study of adult GVHD patients, a total of 17 patients with pulmonary chronic GVHD who received an average of 4 lines of treatment before ibrutinib and had an average of 5 organ involvement were included. Of the 14 patients who continued ibrutinib for 180 days, 2 (14.3%) had a partial response, 9 (64.3%) had a stable disease, and 3 (21.4%) had a disease progression (26). In this study, response rates to ibrutinib may have been found to be low because of the evaluation of the responses of patients with severe pulmonary chronic GVHD with multiple organ involvements and resistant to four lines of therapy. Patients in our study had less organ involvement and none the patients had the pulmonary involvement. Therefore, the response rate to ibrutinib in our study was found to be much higher than that in this study.

Study Limitations

The main limitations of the study are its retrospective design and the small number of patients.

Conclusion

Ibrutinib causes a quite high overall response in steroid resi-resistantnic patients with GVHD and appears to be a good option in these patients. However, prospective trials comparing the effectiveness of ibrutinib with other drugs used in chronic GVHD are needed, especially in lung involvement and/or multiorgan involvement.

Ethics Committee Approval: İnönü University Scientific Research and Publication Ethics Committee (date: 11.01.2022/decision no: 2022/2946).

Informed Consent: Written informed consent was obtained from the patients included in the study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: A.S., İ.K., E.K., A.K., L.H.T.; Design: A.S., M.A.E., E.K., E.H., A.K., Ö.F.B., S.G.Ö.; Data Collection or Processing: A.S., M.A.E., İ.K., E.K., İ.B., E.H., A.K., Ö.F.B., L.H.T.; Analysis or Interpretation: A.S., M.A.E., İ.B., S.B., E.H., A.K.; Literature Search: A.S., İ.K., İ.B., S.B., E.H., A.K.; Writing: A.S., S.B., L.H.T.

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References

1. Trajkovska I, Georgievski B, Cevreska L, Gacovski A, Hasan T, Nedeska-Minova N. Early and Late Complications in Patients with Allogeneic Transplantation of Hematopoietic Stem Cell–Case Report. Open Access Maced J Med Sci 2017; 5: 340.
2. Atilla PA, Atilla E, Toprak SK, Demirer T. Non-infectious early complications of allogeneic stem cell transplantations. UHOD 2016; 29: 239-50.
3. Satwani P, Jin Z, Duffy D, Morris E, Bhatia M, Garvin JH, et al. Transplantation-related mortality, graft failure, and survival after reduced-toxicity conditioning and allogeneic hematopoietic stem cell transplantation in 100 consecutive pediatric recipients. Biol Blood Marrow Transplant 2013; 19: 552-61.
4. Atilla E, Atilla PA, Toprak SK, Demirer T. A review of late complications of allogeneic hematopoietic stem cell transplantations. Clinical transplantation 2017; 31: e13062.
5. Wingard JR, Majhail NS, Brazauskas R, Wang Z, Sobocinski KA, Jacobsohn D, et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. J Clin Oncol 2011; 29: 2230.
6. Bhatia S, Francisco L, Carter A, Sun CL, Baker KS, Gurney JG, et al. Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the Bone Marrow Transplant Survivor Study. Blood 2007; 110: 3784-92.
7. Sarantopoulos S, Cardones AR, Sullivan KM. How I treat refractory chronic graft-versus-host disease. Blood 2019; 133: 1191-200.
8. Jacobsohn DA, Kurland BF, Pidala J, Inamoto Y, Chai X, Palmer JM, et al. Correlation between NIH composite skin score, patient-reported skin score, and outcome: results from the Chronic GVHD Consortium. Blood 2012; 120: 2545-52.
9. Csanadi M, Agh T, Tordai A, Webb T, Jeyakumaran D, Sengupta N, et al. A systematic literature review of incidence, mortality, and relapse of patients diagnosed with chronic graft versus host disease. Expert Rev Hematol 2019; 12: 311-23.
10. Penack O, Marchetti M, Ruutu T, Aljurf M, Bacigalupo A, Bonifazi F, et al. Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. Lancet Haematol 2020; 7: e157-e67.
11. Saad A, de Lima M, Anand S, Bhatt VR, Bookout R, Chen G, et al. Hematopoietic Cell Transplantation, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2020; 18: 599-634.
12. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant 2005; 11: 945-56.
13. Lee SJ, Wolff D, Kitko C, Koreth J, Inamoto Y, Jagasia M, et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. Biol Blood Marrow Transplant2015; 21: 984-99.
14. Lee SJ, Kim HT, Ho VT, Cutler C, Alyea EP, Soiffer RJ, et al. Quality of life associated with acute and chronic graft-versus-host disease. Bone Marrow Transplant 2006; 38: 305-10.
15. Clavert A, Chevallier P, Guillaume T, Delaunay J, Le Gouill S, Mahe B, et al. Safety and efficacy of rituximab in steroid-refractory chronic GVHD. Bone Marrow Transplant 2013; 48: 734-6.
16. Pidala J, Kim J, Roman-Diaz J, Shapiro J, Nishihori T, Bookout R, et al. Pentostatin as rescue therapy for glucocorticoid-refractory acute and chronic graft-versus-host disease. Ann Transplant 2010; 15: 21-9.
17. Lopez F, Parker P, Nademanee A, Rodriguez R, Al-Kadhimi Z, Bhatia R, et al. Efficacy of mycophenolate mofetil in the treatment of chronic graft-versus-host disease. Biol Blood Marrow Transplant 2005; 11: 307-13.
18. Escamilla Gómez V, García-Gutiérrez V, López Corral L, García Cadenas I, Pérez Martínez A, Márquez Malaver FJ, et al. Ruxolitinib in refractory acute and chronic graft-versus-host disease: a multicenter survey study. Bone Marrow Transplant 2020; 55: 641-8.
19. Jurado M, Vallejo C, Pérez-Simón JA, Brunet S, Ferra C, Balsalobre P, et al. Sirolimus as part of immunosuppressive therapy for refractory chronic graft-versus-host disease. Biol Blood Marrow Transplant 2007; 13: 701-6.
20. Arai S, Pidala J, Pusic I, Chai X, Jaglowski S, Khera N,et al. A randomized phase II crossover study of imatinib or rituximab for cutaneous sclerosis after hematopoietic cell transplantation. Clin Cancer Res 2016; 22: 319-27.
21. Couriel DR, Saliba R, Escalón MP, Hsu Y, Ghosh S, Ippoliti C,et al. Sirolimus in combination with tacrolimus and corticosteroids for the treatment of resistant chronic graft-versus-host disease. Br J Hematol 2005; 130: 409-17.
22. Jacobsohn DA, Chen AR, Zahurak M, Piantadosi S, Anders V, Bolaños-Meade J, et al. Phase II study of pentostatin in patients with corticosteroid-refractory chronic graft-versus-host disease. J Clin Oncol 2007; 25: 4255-61.
23. Dubovsky JA, Flynn R, Du J, Harrington BK, Zhong Y, Kaffenberger B, et al. Ibrutinib treatment ameliorates murine chronic graft-versus-host disease. J Clin Invest 2014; 124: 4867-76.
24. Miklos D, Cutler CS, Arora M, Waller EK, Jagasia M, Pusic I, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Blood 2017; 130: 2243-50.
25. Teusink-Cross A, Davies SM, Grimley MS, Chandra S, Flannery A, Dandoy CE, et al. Ibrutinib for the treatment of chronic graft-vs-host disease in pediatric hematopoietic stem cell transplant patients: A single-center experience. Pediatr Transplant 2020; 24: e13692.
26. Singhal S, Brondstetter T, Miklos DB, Tierney DK, Hsu J, Chhatwani L. Ibrutinib for Chronic Pulmonary Graft-Versus-Host-Disease after Progression on Prior Therapy. Blood (2019; 134(Suppl1): 4532.