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ORIGINAL RESEARCH REPORT

A Single-center, Real-world Experience of Chronic GVHD Treatment Using Ibrutinib, Imatinib, and Ruxolitinib and its Treatment Outcomes

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Abstract

Background: **Chronic graft-versus-host disease (cGVHD) is a common cause of morbidity and mortality following allogeneic hematopoietic stem cell transplantation. Tyrosine kinase inhibitors (TKIs), including ruxolitinib, imatinib, and ibrutinib, have shown promising efficacy in cGVHD treatment.**

Method: **A total of 43 patients who developed cGVHD and received at least one line of TKI therapy for cGVHD treatment were evaluated retrospectively. The overall response, clinical benefit (CB), corticosteroid dose reduction, failure-free survival (FFS), and overall survival (OS) were assessed.**

Result: **A total of 62 lines of TKI therapy were evaluated, including ruxolitinib (n = 18), ibrutinib (n = 13), and imatinib (n = 31). With a 12-month median follow-up duration, 19/58 (32.8%), 20/41 (48.7%), and 17/29 (58.6%) responded to TKI therapy at 3, 6, and 12 months, respectively. The CB was observed in 80% of patients over time, allowing prednisone dose reduction in all 3 TKIs. The FFS rate at 12 months was higher in the imatinib (71%) and ruxolitinib groups (67%) than in the ibrutinib group (46%), while the OS rate at 12 months was similar among the three groups at 96%−100% in patients. In the sclerotic GVHD patient subgroup (n = 39), the overall response rate gradually increased over time. Ruxolitinib appeared to be as effective as imatinib and gradually improved the photographic range of motion score in sclerotic GVHD patients.**

Conclusion: **TKI drugs ruxolitinib, imatinib, and Ibrutinib are effective and feasible for cGVHD treatment. Ruxolitinib is as effective as imatinib for sclerotic GVHD.**

Keywords: Chronic graft versus host disease, Tyrosine kinase inhibitors

1. Introduction

Chronic graft-versus-host-disease (cGVHD) is a frequently observed cause of morbidity and mortality following allogeneic hematopoietic stem cell transplantation (HCT) [1]. Despite the use of standard GVHD prophylaxis, a significant proportion of patients develop cGVHD, requiring prolonged systemic immunosuppression [1−3]. Several cGVHD treatment options have been developed, including novel monoclonal antibodies [4−7], targeted molecule inhibitors [8−10], and IL-2 [11−13] and cellular therapies [14,15], while some are currently in clinical trials [16].

Tyrosine kinase inhibitors (TKIs) block molecular targets which are involved in biological pathways of

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cancer [8] and additionally inhibit cytokine production/regulation and inflammation affecting T- or B cell activation in cGVHD pathogenesis [16,17]. T and B cells are known to play a critical role in the pathogenesis of cGVHD [18–20]. Accordingly, TKIs, including ruxolitinib, ibrutinib, and imatinib, have been introduced in the treatment of cGVHD and shown promising efficacy.

Ruxolitinib, a JAK-STAT inhibitor, reduces systemic inflammation in GVHD via blockade of the JAK-STAT pathway, inhibiting donor T-cell expansion and inflammatory cytokine production and affecting regulatory T-cell function and viability [21]. It is an effective treatment option for both acute and chronic GVHD [21,22] and was approved by the US FDA on September 22, 2021, for the treatment of cGVHD after the failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older [23].

Increased B-cell receptor (BCR) responsiveness has been observed in patients with cGVHD and has represented an attractive therapeutic target. Ibrutinib is a selective inhibitor of Bruton's tyrosine kinase predominantly expressed in B cells [24]. It prevents signal transduction from BCR by inhibiting B cell-activating factor, a member of the tumor necrosis family [25,26]. Ibrutinib was the first FDA-approved TKI drug for cGVHD therapy for adult patients with cGVHD after the failure of one or more lines of systemic therapy [27].

Imatinib inhibits both TGF-β and platelet-derived growth factor-mediated pathways activated by cGVHD-induced antibodies. It is effective in a subtype of chronic GVHD presenting mainly with fibrotic features [28–30]. Imatinib was the first generation TKI targeting the BCR-ABL fusion kinase and has been used for over two decades, primarily for treating Philadelphia-positive leukemias. Imatinib has also been used off-label in cGVHD treatment, showing significant clinical activity with improvement in the severity of cGVHD, particularly in skin fibrosis [31].

Accordingly, the present study analyzed our real-world experience of TKI therapy for cGVHD as second-line or beyond and evaluated the outcomes of TKI therapies. In addition to overall response rate (ORR) and clinical benefit (CB), failure-free survival (FFS) was applied in the present study, which is currently considered a relevant endpoint for the efficacy of chronic GVHD treatment [32]. This study evaluated the efficacy of three TKIs for cGVHD treatment for five parameters, namely 1) ORR, 2) CB, 3) dose reduction of steroids, 4) FFS, and 5) OS.

2. Patients and Methods

2.1. Patient characteristics and treatment

In this retrospective study, 62 lines of TKI therapy were evaluated, including ruxolitinib (n = 18), ibrutinib (n = 13), and imatinib (n = 31), in 43 patients who were treated for cGVHD at Princess Margaret Cancer Centre, Canada, from August 2014 to April 2021. Sixteen patients were treated with more than one TKI drug. We defined each treatment line with one TKI drug as a separate case. Thus, out of 62 cases, 26 were treated with a single TKI, 30 were treated with 2 TKIs, and 6 were treated with 3 TKIs.

Patients treated with TKIs after HCT specifically for primary hematologic malignancies such as chronic myeloid leukemia and chronic lymphocytic leukemia were excluded; those not evaluated for ORR or CB at 3 months were excluded from the analysis. The National Institute of Health (NIH) consensus criteria for cGVHD were applied for the diagnosis of cGVHD, scoring of cGVHD organ involvement, and assessing the global severity of cGVHD [33]. This study was approved by the Research Ethics Board of the University Health Network, Toronto, Canada. The clinical data were locked as of April 2021.

cGVHD treatment was decided after considering the individual patient's clinical status. Steroid therapy was used as the first-line regimen for patients not receiving immunosuppressants. When front-line therapy with prednisone with or without cyclosporine failed, second-line therapy, including tacrolimus, MMF, extracorporeal photopheresis (ECP), hydroxychloroquine, or azathioprine, was attempted [34]. If the patient failed to respond to the potential GVHD treatment, TKI therapy was considered a third or fourth line of treatment. We now consider ruxolitinib a second-line option. The choice of TKI drug is mainly based on the underlying disease, type of cGVHD, comorbidities, and potential toxicity profiles. For example, in patients with underlying B cell malignancies such as chronic lymphocytic leukemia, ibrutinib is preferred because it can be easily reimbursed; imatinib is preferred in patients without any further option for sclerotic GVHD or those with an underlying diagnosis of CML or Ph + ALL. Ruxolitinib was also preferred in patients with a history of myelofibrosis or myeloproliferative neoplasm. Ruxolitinib should be avoided in patients with existing cytopenia. Patients with a bleeding tendency or QTc prolongation were not candidates for Ibrutinib.

2.2. Response assessment

The ORRs and CBs were assessed retrospectively at months 3, 6, and 12. Responses were evaluated according to NIH response assessment as part of standard clinical practice with complete and partial responses per NIH criteria combined for an ORR in any affected organ [35]. Where the NIH score changes were not delineated in the medical record, these were assigned retrospectively based on descriptions in the clinical notes. The overall response was defined as the attainment of complete response (CR) in all involved organs without evidence of progressive disease (PD) in any organ; overall partial response (PR) was defined as the presence of PR in at least one involved organ without evidence of PD in any organ; overall PD was defined as the presence of PD in any organ or any new organ involvement; and overall stable disease (SD) was defined as none of the above.

CB was assessed considering the clinical response and steroid dose reduction. CB was defined as follows: (1) very beneficial - CR regardless of prednisone dose reduction or PR with significant dose reduction in prednisone (>50%), (2) beneficial - PR with a reduction in prednisone dose (<50%) or SD with a significant reduction in prednisone dose (>50%), (3) minor benefit - SD with a minor reduction in prednisone dose (<50%), (4) no benefit - progression or no change/increase in prednisone dose. For subgroup analysis in those having sclerotic GVHD, longitudinal changes in the photographic range of motion (PROM) score were evaluated with the PROM score measured at each time point.

2.3. Daily steroid dose considering body weight

To assess systemic steroid dose reduction, daily prednisone dose per body weight in kg was captured prior to the start of TKI at months 3, 6, and 12. The prednisone dose was compared according to the achievement of CB at months 3, 6, and 12 and among the different TKI drugs. The proportion of patients with prednisone dose $\leq$0.5 mg/kg/day, $\leq$0.2 mg/kg/day, $\leq$0.1 mg/kg/day, and 0 was calculated at months 0, 3, 6, and 12, respectively, and compared.

Table 1. Summary of patients, disease, and GVHD characteristics

		Overall	Ruxolitinib	Ibrutinib	Imatinib	p-value
Demographics		N = 62	N = 18	N = 13	N = 31	
Age, median (range)	Years	54 (16–70)	50.5 (22–70)	53.5 (27–67)	55 (16–68)	0.392*
Sex	Male	29 (47)	7 (39)	5 (39)	17 (55)	0.445
	Female	33 (53)	11 (61)	8 (61)	14 (45)	
Transplant procedure						
Conditioning	MAC	42 (68)	10 (56)	9 (69)	23 (74)	0.430
	RIC	20 (32)	8 (44)	4 (31)	8 (26)	
Donor	MRD	32(51)	6 (33)	7 (54)	19 (61)	0.172
	MUD	24 (39)	8 (44)	5 (38)	11 (36)	
	9/10 and haplo	6 (10)	4 (22)	1 (8)	1 (3)	
Post-transplant events						
Acute GVHD	Yes	32 (52)	9 (50)	6 (46)	17 (55)	0.844
Chronic GVHD, at initial presentation						
Subtype	Classical	33 (53)	8 (44)	6 (46)	19 (61)	0.478
	Overlap	29 (47)	10 (56)	7 (54)	12 (39)	
Severity	Moderate	56 (90)	16 (89)	12 (92)	28 (90)	1.000
	Severe	6 (10)	2 (11)	1 (8)	3 (10)	
No. of organ, involved		2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	0.209
Organ involvement prior to TKI therapy	Skin	43 (69)	9 (50)	10 (77)	24 (77)	0.115
	Mouth	25 (40)	6 (33)	5 (39)	14 (45)	0.705
	Eye	18 (29)	4 (22)	4 (31)	10 (32)	0.748
	GI	17 (27)	4 (22)	4 (31)	9 (29)	0.836
	Liver	28 (45)	13 (72)	5 (39)	10 (32)	0.019
	Lung	25 (40)	5 (28)	6 (46)	14 (45)	0.490
	Musculoskeletal	41 (66)	9 (50)	9 (69)	23 (74)	0.246
	Others	7 (11)	3 (17)	1 (8)	3 (10)	0.764

***Abbreviations**: MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; MRD, matched related donor; MUD, matched unrelated donor; GI, gastrointestinal.

2.4. Survival endpoints

OS was defined as the date from starting TKI therapy for cGVHD to the date of death from any cause or last follow-up. FFS was defined as the time from beginning TKI therapy for cGVHD to treatment failures. Treatment failure was defined as (1) treatment switch due to resistance or intolerance to treatment, (2) non-relapse mortality (NRM), or (3) relapse of the primary disease. FFS and OS were calculated using Kaplan–Meier estimates.

2.5. Statistical analysis

Demographic and transplant procedure-related characteristics and GVHD-related characteristics, including cGVHD severity, organ involvement, previous therapy, and response to previous GVHD treatment, were analyzed and compared using Chi-square, Fisher's exact, or Kruskal–Wallis tests among the three groups. The ORR and CB were evaluated using the Chi-square test. Prednisone dose reduction was analyzed using Student's t-test; the proportion of the patients on certain dose levels of daily prednisone was also compared using the Chi-square test. The OS and FFS were calculated using the Kaplan–Meier method with the log-rank test. Hazard ratios and 95% confidence intervals were estimated for the significant risk factors, with a statistical significance level of 0.05. Statistical analyses were performed using EZR software (version 1.55, Saitama Medical Center, Jichi Medical University, Saitama, Japan, http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html.) [36]

3. Results

3.1. Patient and disease characteristics at the time of initial presentation of chronic GVHD

The patient and disease characteristics are summarized in Table 1. A total of 62 lines of TKI therapy were delivered to 43 patients. The transplant and cGVHD disease characteristics are described based on the 62 cases treated.

The median patient age was 54 (range 16–70); 29 (47%) were male. Forty-two patients (68%) received a preparatory myeloablative conditioning regimen, and twenty (32%) received reduced-intensity conditioning regimens. Thirty-two (51%) recipients were transplanted from a related donor, twenty-four (39%) from a matched unrelated donor, three (5%) from a haplo-identical donor, and three (5%) from 9/10 mismatched unrelated donors.

At the time of initial presentation of cGVHD, 32 (52%) had a previous history of acute GVHD. Thirty-three (53%) cases presented with classical cGVHD, while twenty-nine (47%) developed overlap syndrome; there was no difference in the cGVHD subtype among the three TKI subgroups ($p = 0.478$). In terms of cGVHD severity at initial presentation of cGVHD, 56 (90%) had moderate

Table 2. Summary of disease characteristics and GVHD treatments prior to TKI therapy

	Overall	Ruxolitinib	Ibrutinib	Imatinib	p-value
	N = 62	N = 18	N = 13	N = 31	
Previous therapy for chronic GVHD					
Prednisone	62 (100)	18 (100)	13 (100)	31 (100)	–
Cyclosporine	39 (63)	11 (61)	10 (77)	18 (58)	0.541
Tacrolimus	11 (18)	3 (17)	2 (15)	6 (19)	1.000
Mycophenolate	46 (74)	11 (61)	11 (85)	24 (77)	0.323
ECP	41 (66)	11 (61)	9 (69)	21 (68)	0.881
Azathioprine	44 (71)	11 (61)	10 (77)	23 (74)	0.617
Hydroxychloroquine	27 (44)	5 (28)	6 (46)	16 (52)	0.293
Response to the previous treatment					
Steroid-resistant	50 (81)	16 (89)	9 (69)	25 (81)	0.649
Steroid-dependent	9 (14)	2 (11)	3 (23)	4 (13)	
Intolerant	3 (5)	0 (0)	1 (8)	2 (6)	
Chronic GVHD severity					
Moderate grade	14 (23)	4 (22)	3 (23)	7 (23)	1.000
Severe grade	48 (77)	14 (78)	10 (77)	24 (77)	
No. of organ involved	4 (1–5)	3.5 (1–5)	4 (1–5)	4 (1–5)	0.209

*Abbreviations: GI, gastrointestinal; S.E, standard error; ECP, extracorporeal electrophoresis.

grade, and 6 (10%) had severe grade cGVHD, while there was no difference among the TKI subtypes (p = 1.0). At the time of the initial presentation of cGVHD, the median number of organs involved was 2 (range 1–3).

3.2. Previous treatment and the reason for failure to prior line therapy for cGVHD treatment

All 62 patients (100%) had previously been treated with systemic corticosteroids, followed by mycophenolate (n = 46, 74%), azathioprine (n = 44, 71%), ECP (n = 41; 66%), cyclosporine (n = 39, 63%), hydroxychloroquine (n = 27, 44%), or tacrolimus (n = 11, 18%). Prior therapies for each TKI drug are summarized in Supplementary Figure 1. Fifty cases (80%) were steroid-resistant, while nine cases (14%) were steroid-dependent, and three cases (5%) were intolerant to corticosteroids.

The GVHD characteristics and prednisone doses before the TKI therapy are summarized in Table 2. All patients had moderate (n = 14, 23%) or severe grade cGVHD (n = 48, 77%) before starting TKI therapy; no difference in cGVHD severity was noted according to TKI subtypes (p = 1.0). The median number of organ involvement before TKI therapy was 4 (range 1–5). The most frequently involved organ site prior to TKI therapy was the skin (n = 43, 69%), followed by the musculoskeletal system (i.e., sclerotic GVHD; n = 41, 66%), liver (n = 28, 45%), mouth (n = 25, 40%), lungs (n = 25, 40%), eyes (n = 18, 29%), gastrointestinal tract (n = 17, 27%), and others (n = 7, 11%). The details of organ involvement for each TKI drug are summarized in Supplementary Figure 2.

3.3. Treatment details including daily dose of TKI drugs and corticosteroid

The mean daily dose of TKIs (± standard error) was as follows: ruxolitinib was started at 15 ± 1.1 mg as the initial dose and delivered at 20 ± 0.7, 19 ± 1.5, and 22 ± 4.4 mg per day in two divided doses on months 3, 6, and 12, respectively. Ibrutinib was given at the daily dose of 226 ± 37, 256 ± 37, 308 ± 40, and 370 ± 33 mg per day, while the daily imatinib dose was 106 ± 6, 189 ± 18, 196 ± 16, and 190 ± 19 mg per day at the initial treatment and months 3, 6, and 12, respectively.

3.4. ORR and CB of TKI therapy for chronic GVHD treatment

The treatment outcomes for ORR are summarized in Table 3. With a median follow-up duration

Table 3. Summary of treatment outcomes among Ruxolitinib-, Ibrutinib-, and Imatinib-treated patients

No. of pts (%)	Ruxolitinib				Ibrutinib			Imatinib		
	0 months	3 months	6 months	12 months	0 months	3 months	6 months	0 months	3 months	6 months	12 months
Overall response	–	N = 14	N = 5	N = 4	–	N = 13	N = 9	–	N = 31	N = 27	N = 22
CR		0 (0)	0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	1 (4)	0 (0)
PR		8 (57)	4 (80)	3 (75)		3 (27)	4 (44)		8 (26)	11 (41)	12 (54)
SD		4 (29)	0 (0)	1 (25)		8 (73)	3 (33)		20 (64)	12 (44)	5 (23)
PD		2 (14)	1 (20)	0 (0)		0 (0)	2 (22)		3 (10)	3 (11)	5 (23)
Clinical benefits	–	N = 11	N = 5	N = 4	–	N = 11	N = 9	–	N = 31	N = 27	N = 22
Very beneficial		0 (0)	0 (0)	0 (0)		1 (9)	1 (11)		0 (0)	0 (0)	0 (0)
Beneficiald		6 (55)	3 (60)	3 (75)		1 (9)	3 (33)		9 (30)	14 (52)	13 (59)
Minor benefit		4 (36)	2 (40)	1 (25)		8 (72)	3 (33)		18 (60)	8 (30)	4 (18)
No benefit		1 (9)	0 (0)	0 (0)		1 (9)	2 (22)		3 (10)	5 (18)	5 (23)
Prednisone dose reduction, No pts	N = 18	N = 14	N = 9	N = 3	N = 13	N = 12	N = 10	N = 30	N = 31	N = 27	N = 21
≤0.5 mg/kg/day	17 (94)	14 (100)	8 (89)	3 (100)	10 (77)	11 (92)	10 (100)	25 (83)	29 (94)	26 (96)	21 (100)
≤0.2 mg/kg/day	9 (50)	11 (79)	5 (56)	2 (67)	6 (46)	8 (67)	7 (70)	16 (53)	19 (61)	21 (78)	20 (95)
≤0.1 mg/kg/day	4 (22)	8 (57)	5 (56)	1 (33)	4 (31)	5 (42)	4 (40)	13 (43)	14 (45)	15 (56)	13 (62)
0 mg/kg/day	4 (22)	4 (29)	1 (11)	0 (0)	3 (23)	3 (25)	3 (30)	1 (25)	9 (30)	10 (37)	7 (33)

*Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

of 12 months, ORR was observed in 19 out of 58 patients (32.8%) at 3 months, 20 out of 41 (48.7%) at 6 months, and 17 out of 29 (58.6%) at 12 months (Fig. 1). Approximately 80% of patients achieved CB over time up to 12 months; 47 out of 53 (88.6%) achieved CB at 3 months, 34 out of 41 (82.9%) at 6 months, and 23 out of 29 (79.3%) achieved CB at 12 months (Fig. 2). No difference in ORR or CB was noted among the TKI drug subtype in this cohort.

3.5. Daily corticosteroid dose reduction

The daily dose of prednisone was gradually reduced over 12 months: the daily dose of prednisone (mg/kg/day) was 0.238 ± 0.03 prior to the start of TKI and was gradually reduced to 0.177 ± 0.03 at 3 months, 0.173 ± 0.03 at 6 months, and 0.110 ± 0.02 at 12 months.

The prednisone dose reductions divided by the three TKIs are compared and summarized in Fig. 3. No statistically significant difference was noted in the daily corticosteroid dose among the three TKIs at each time point; at three months, the daily corticosteroid doses per kg were as follows: 0.207 ± 0.07, 0.135 ± 0.03, and 0.183 ± 0.03 in the ruxolitinib, ibrutinib, and imatinib groups ($p = 0.949$), respectively. At six months, the daily corticosteroid doses were: 0.143 ± 0.04, 0.249 ± 0.11, and 0.152 ± 0.04 in the ruxolitinib, ibrutinib, and imatinib groups ($p = 0.667$), respectively. At 12 months: 0.142 ± 0.06, 0.160 ± 0.07, and 0.094 ± 0.02 in the ruxolitinib, ibrutinib, and Imatinib groups ($p = 0.518$), respectively (Table 4 and Fig. 3).

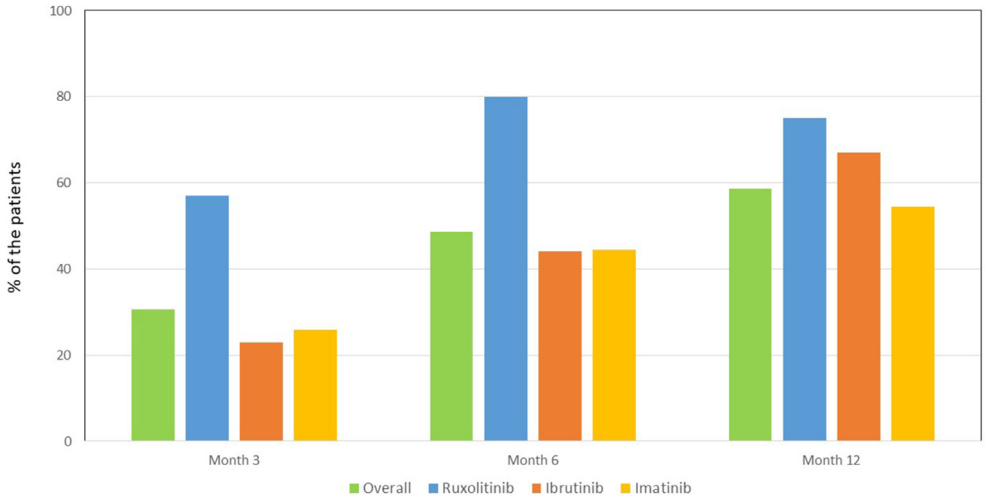

Fig. 1. Overall response rate at months 3, 6, and 12 in the overall population and the subgroups treated with ruxolitinib, ibrutinib, and imatinib.

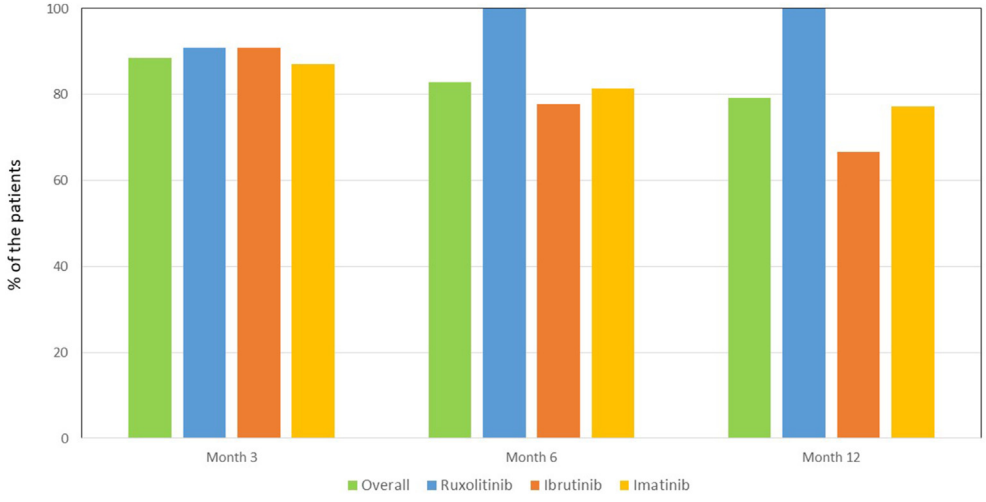

Fig. 2. Clinical benefit at months 3, 6, and 12 in the overall population and the subgroups treated with ruxolitinib, ibrutinib, and imatinib.

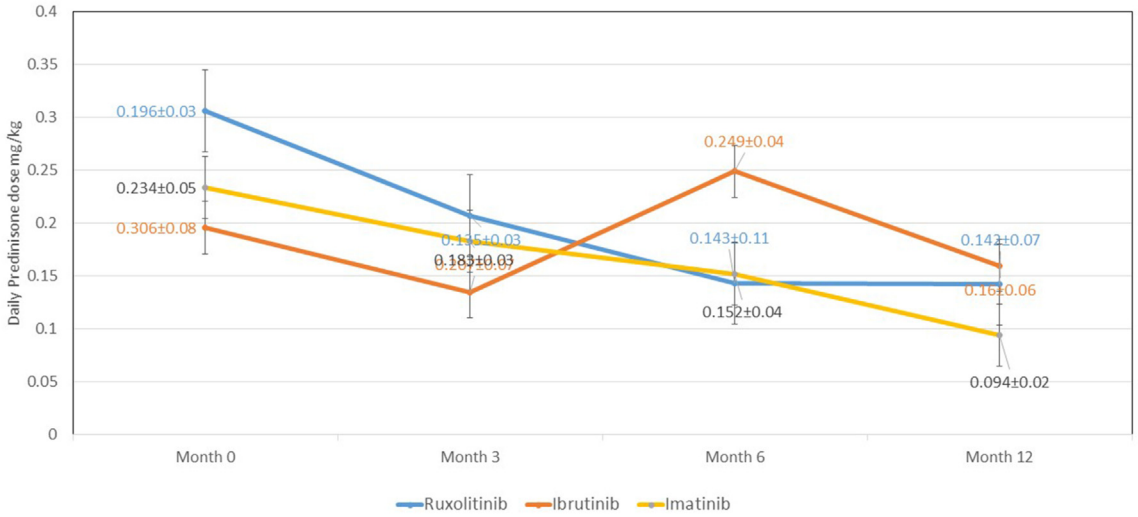

Fig. 3. Daily prednisone dose reduction and its serial changes prior to TKI start and at months 3, 6, and 12 according to the TKI drug subtype (ruxolitinib, ibrutinib, and imatinib).

In general, as shown in Table 3, all patients (100%) were able to reduce their daily prednisone dose below 0.5 mg/kg/day at 12 months in all 3 groups; 67–95% reduced it to ≤0.2 mg/kg/day, and 25–62% to ≤0.1 mg/kg/day at 12 months. A total of 5 out of 18 (27%), 7 out of 13 (54%), and 26 out of 31 patients (84%) treated with ruxolitinib, ibrutinib, and imatinib, respectively, discontinued prednisone by 12 months.

Table 4. Summary of daily Prednisone dose reduction over time

	Overall	Ruxolitinib	Ibrutinib	Imatinib	p-value
Prior to TKI therapy	**N = 61**	**N = 18**	**N = 13**	**N = 30**	
Dose, median (range)	–	20 mg (10–20)	140 mg (140–420)	100 mg (100–300)	–
Mean ± S.E. (mg/day)	–	15 ± 1.1	226 ± 37	106 ± 6	–
Prednisone, mg/kg/day	0.238 ± 0.03	0.306 ± 0.08	0.196 ± 0.03	0.234 ± 0.05	0.700*
Dose at 3 months	**N = 55**	**N = 12**	**N = 12**	**N = 31**	
Dose, median (range)	–	20 mg (15–30)	280 mg (140–420)	200 mg (100–400)	–
Mean ± S.E. (mg/day)	–	20 ± 0.7	256 ± 37	189 ± 18	–
Prednisone, mg/kg/day	0.177 ± 0.03	0.207 ± 0.07	0.135 ± 0.03	0.183 ± 0.03	0.949*
Dose at 6 months	**N = 44**	**N = 9**	**N = 10**	**N = 25**	
Dose, median (range)	–	20 mg (10–30)	420 mg (140–420)	200 mg (100–400)	–
Mean ± S.E. (mg/day)	–	19 ± 1.5	308 ± 40	196 ± 20	–
Prednisone, mg/kg/day	0.173 ± 0.03	0.143 ± 0.04	0.249 ± 0.11	0.15197 ± 0.04	0.667*
Dose at 12 months	**N = 25**	**N = 3**	**N = 4**	**N = 18**	
Dose, median (range)	–	20 mg (15–30)	420 mg (280–420)	200 mg (100–400)	–
Mean ± S.E. (mg/day)	–	22 ± 4.4	370 ± 33	190 ± 19	–
Prednisone, mg/kg/day	0.110 ± 0.02	0.142 ± 0.06	0.160 ± 0.07	0.094 ± 0.02	0.518*
Failure	**N = 62**	**N = 18**	**N = 13**	**N = 31**	
No failure	33 (53)	17 (94)	5 (39)	11 (35)	
Treatment switch	27 (44)	1 (6)	8 (61)	18 (58)	
NRM	2 (3)	0 (0)	0 (0)	2 (7)	
Relapse	0 (0)	0 (0)	0 (0)	0 (0)	
Discontinuation	28 (44)	1 (6)	8 (62)	18 (58)	0.001
Follow-up (months)	10.5 (1–70)	7 (1–39)	8.5 (1–68)	19.2 (3–70)	0.016*
Mortality	3 (5)	0 (0)	1 (8)	2 (6)	0.587
FFS rate at 12 months (%)	98.3 (88.4–99.8)	93.3 (61.3–99.0)	46.2 (19.2–69.6)	67.6 (48.1–81.1)	0.113
OS rate at 12 months (%)	66.8 (52.3–77.7)	96.8 (79.2–99.5)	100.0(NA–NA)	100.0 (NA–NA)	0.755

*Kruskal–Wallis test for non-parametric test.
Abbreviations: NRM, non-relapse mortality; FFS, failure-free survival; OS, overall survival.

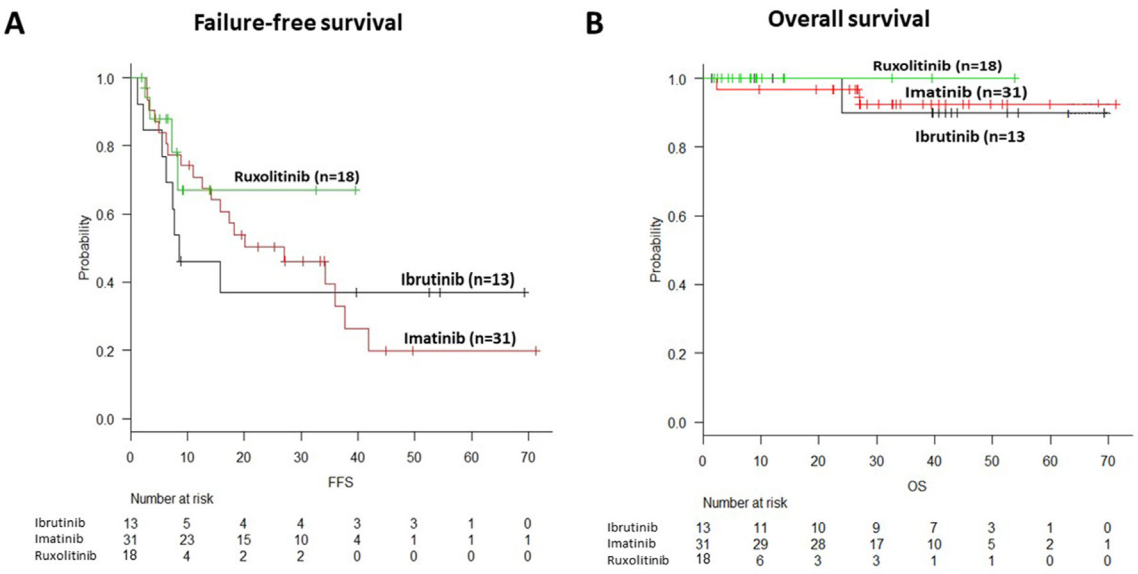

Fig. 4. Failure-free (A) and overall survival (B) according to the TKI drug subtype (ruxolitinib, ibrutinib, and imatinib).

3.6. FFS and OS

FFS and OS are summarized in Table 4. Among 62 patients, 27 (44%) required a treatment switch to additional therapy, 2 (3%) developed NRM, while none of the patients relapsed their primary disease: 1 case treated with ibrutinib and imatinib died of secondary malignancy; another case treated with imatinib died of organ failure contributed by cGVHD. The FFS at 12 months was higher in the group treated with imatinib (71%) or ruxolitinib (67%) than in the group treated with ibrutinib (46%) ($p = 0.113$) (Fig. 4A). The OS rate at 12 months was similar: 100% in the ruxolitinib and ibrutinib groups and 96% in the imatinib group ($P = 0.755$) (Fig. 4B).

3.7. Treatment outcomes in the subgroup of patients with sclerotic GVHD

Treatment outcomes in the subgroup of patients with sclerotic GVHD ($n = 39$) are summarized in Table 5: the ORR was 11/39 (28%), 15/39 (38%), and 13/39 (33%) for 3, 6, and 12 months, while CB was noted in 32/39 (82%), 25/39 (64%), and 16/39 cases (41%) at 3, 6, and 12 months respectively.

The PROM scores before TKI start and at 3, 6, and 12 months were 17.8 ± 1.3, 17.8 ± 0.8, 20.3 ± 0.9, and 22.0 ± 1.0 with ruxolitinib ($n = 8$) and 19.7 ± 1.0, 20.1 ± 1.0, 19.8 ± 1.2, and 21.4 ± 1.5 with imatinib ($n = 23$), respectively. The changes in PROM score with ibrutinib ($n = 8$) were 17.6 ± 1.9, 18.4 ± 2.1, 18.0 ± 1.6, and 18.0 ± 0, respectively. Interestingly, ruxolitinib was as effective as imatinib in improving PROM scores in sclerotic GVHD patients. In contrast, no significant improvement in PROM score was observed in patients treated with ibrutinib for sclerotic GVHD.

4. Discussion

The present study presents the real-world experience of TKIs for cGVHD treatment in heavily pretreated patients who failed previous lines of cGVHD therapy and evaluated its efficacy. The ORR was higher with ruxolitinib at 57%, 80%, and 75% ORR at 3, 6, and 12 months, respectively, compared with ORR at week 24 in the ruxolitinib arm of 49.7% in the REACH 3 study [37]. A recent study by Wang et al. showed 74% ORR at 24 weeks in 70 patients who received ruxolitinib as salvage therapy for SR-cGVHD, which is comparable with our results [38]. Previous studies have documented responses as early as day 28: a retrospective study by Abedin et al. reported a 63% response rate at approximately 28 days of ruxolitinib treatment in cGVHD [39]. Similar results were reported by Gomez et al., where an ORR of 57% in 56 patients was noted at 4 weeks following ruxolitinib treatment [21]. Thus, our results from a real-world experience in heavily pretreated cGVHD patients appear comparable with others.

For other TKIs, the ORR for the ibrutinib group was calculated as 67%, comparable with a multicenter study led by Miklos et al. showing a best overall response of 67% at a median follow-up of 13.9 months [26], and Doki et al. showing 73% ORR at a median of 9 months of ibrutinib treatment.

Table 5. Treatment outcomes in the patients with a sclerotic form of musculoskeletal GVHD and treated with TKI therapy

No. of pts (%)	Ruxolitinib (n = 8)				Ibrutinib (n = 8)				Imatinib (n = 23)			
	0 months	3 months	6 months	12 months	0 months	3 months	6 months	12 months	0 months	3 months	6 months	12 months
Overall response	–	N = 8	N = 4	N = 3	–	N = 8	N = 6	N = 3	–	N = 23	N = 20	N = 15
CR		0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	2 (67)		0 (0)	1 (5)	0 (0)
PR		2 (20)	3 (75)	2 (67)		3 (37)	3 (50)	0 (0)		6 (26)	8 (40)	9 (60)
SD		4 (50)	0 (0)	1 (33)		5 (63)	2 (33)	1 (33)		15 (65)	9 (45)	2 (13)
PD		2 (25)	1 (25)	0 (0)		0 (0)	1 (17)	0 (0)		2 (9)	2 (10)	4 (27)
Clinical benefits	–	N = 6	N = 4	N = 3	–	N = 8	N = 6	N = 3	–	N = 22	N = 20	N = 15
Very beneficial		0 (0)	0 (0)	0 (0)		1 (13)	1 (17)	0 (0)		0 (0)	0 (0)	0 (0)
Beneficial		1 (17)	2 (50)	2 (67)		1 (13)	2 (33)	2 (67)		6 (27)	9 (45)	9 (60)
Minor benefit		4 (67)	2 (50)	1 (33)		5 (62)	2 (33)	0 (0)		14 (64)	7 (35)	2 (13)
No benefit		1 (17)	0 (0)	0 (0)		1 (13)	1 (17)	1 (33)		2 (9)	4 (20)	4 (27)
Reduction in Prednisone dose (No. of pts)	N = 9	N = 6	N = 4	N = 2	N = 9	N = 9	N = 7	N = 4	N = 22	N = 23	N = 19	N = 13
Prednisone (mg/kg/day)	0.12 ± 0.04	0.14 ± 0.05	0.11 ± 0.06	0.10 ± 0.06	0.21 ± 0.07	0.22 ± 0.09	0.13 ± 0.05	0.14 ± 0.06	0.23 ± 0.06	0.19 ± 0.05	0.12 ± 0.04	0.07 ± 0.03
≤0.5 mg/kg/day	9 (100)	8 (100)	4 (100)	2 (100)	8 (80)	8 (89)	7 (100)	4 (100)	18 (82)	21 (91)	20 (100)	14 (100)
≤0.2 mg/kg/day	7 (78)	6 (75)	3 (75)	2 (100)	5 (56)	6 (67)	5 (71)	3 (75)	13 (59)	14 (61)	15 (75)	13 (93)
≤0.1 mg/kg/day	3 (33)	4 (50)	3 (75)	1 (50)	3 (33)	4 (44)	3 (43)	1 (25)	10 (46)	10 (44)	12 (60)	10 (71)
0 mg/kg/day	3 (33)	4 (50)	1 (25)	0 (0)	3 (33)	4 (33)	3 (43)	1 (25)	7 (32)	7 (30)	8 (40)	5 (36)
PROM, No. of pts evaluated	8	6	3	2	8	8	4	2	19	19	17	10
PROM score (mean ± S.E.)	17.8 ± 1.3	17.8 ± 0.8	20.3 ± 0.9	22.0 ± 1.0	17.6 ± 1.9	18.4 ± 2.1	18.0 ± 1.6	18.0 ± 0	19.7 ± 1.0	20.1 ± 1.0	19.8 ± 1.2	21.4 ± 1.5

*Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PROM, photographic range of motion.

Thus, we confirmed a similar therapeutic efficacy of ibrutinib for cGVHD therapy for ORR.

In our study, a new metric, CB, was introduced for assessing the clinical efficacy of cGVHD treatment, which is a composite parameter including NIH criteria-based overall response and daily steroid dose reduction. Due to the nature of the fibrotic pathobiology of chronic GVHD, CR is rarely expected to be observed in heavily pretreated patients with longstanding severe-grade chronic GVHD and with clinical manifestations such as scleroderma and bronchiolitis obliterans, which are often irreversible. However, the ability to reduce and taper the systemic corticosteroid provides tremendous clinical merit for patients on this treatment, thus reducing the risk of metabolic and infectious complications associated with its long-term use. While the response assessment using the NIH consensus response criteria helps evaluate the reversal of organ damage in cGVHD-affected tissue, it does not incorporate steroid tapering in the therapeutic benefit assessment. Hence, by considering steroid dose reduction as part of the therapeutic benefit assessment, our CB outcome provides a more global evaluation of the therapeutic benefit of cGVHD treatment, overcoming some of the limitations in NIH criteria in the response assessment of cGVHD treatment. Over time, we observed approximately 80% CB in our patients for all three TKI drugs.

In the current study, all three TKI groups gradually reduced the prednisone dose over time. This is important since prolonged corticosteroid treatment contributes to a profoundly immunodeficient state, increasing the risk of severe, life-threatening, or fatal infectious complications [30]. Consistent with the present study, Khoury et al. and Ferreira et al. demonstrated that ruxolitinib is an effective corticosteroid-sparing agent in cGVHD [40,41]. However, in the current study, the ibrutinib group required a higher daily dose of prednisone, particularly at six months, than the ruxolitinib or imatinib groups, as shown in Fig. 3. Miklos et al. reported the clinically meaningful result that in ibrutinib-treated patients, the median corticosteroid dose in responders decreased from 0.29 mg/kg/day at the baseline to 0.12 mg/kg/day at 12 months, and that five responders discontinued corticosteroids. In our study, ibrutinib-treated patients showed a reduction in daily prednisone dose from 0.306 mg/kg/day at the baseline to 0.142 mg/kg/day at 12 months, and 7/13 responders discontinued prednisone at 12 months.

In all three TKIs evaluated, a rapid tapering of corticosteroids was observed. Approximately 25–62% of patients could decrease prednisone to ≤0.1 mg/kg/day at 12 months, while 62%, 75%, and

78% of patients treated with ruxolitinib, ibrutinib, and imatinib, respectively, discontinued corticosteroids at 12 months. Modi et al. showed an association of ruxolitinib with a reduction in prednisone dose in cGVHD, and Khoury et al. described the reduction to physiologic doses or discontinuation of prednisone in 90% of patients treated with ruxolitinib [41,42]. Thus, our findings are consistent with previous reports [41,42].

FFS was also evaluated as a parameter to assess the clinical efficacy of TKI drugs. FFS is a composite endpoint including treatment failure requiring therapy switch, non-relapse mortality, and recurrence of primary hematologic malignancy. It has been widely used as an alternative statistical endpoint in clinical trials for cGVHD [32]. In the current study, the 12-month FFS rate was superior in the imatinib (71%) and ruxolitinib (67%) groups than in the ibrutinib group (46%). The FFS in the ruxolitinib group at 12 months was comparable with the one-year probability of 54% FFS (95% CI, 0.388 to 0.673) by Modi et al. [42] However, there are limited studies on evaluating FFS in ibrutinib-treated cGVHD patients. A single-center experience reported a two-year FFS of 9% after initiating ibrutinib with a median FFS of 4.5 months [43]. Our experience also confirmed that the FFS with ibrutinib is somewhat lower than the FFS of cGVHD patients treated with imatinib or with ruxolitinib.

Given the limited data on TKI treatment outcomes in sclerotic GVHD, we specifically analyzed this manifestation, particularly for PROM score changes. Sclerotic GVHD is one of the most severe forms of GVHD affecting the quality of life of patients and is frequently refractory to standard treatment approaches [44]. Thus, it often requires a significantly prolonged duration of intensive immunosuppressive treatment. In the current study, we observed a significant improvement in the range of movement as measured with the PROM score. Ruxolitinib was as effective as imatinib in improving PROM. In addition, our data revealed an ORR of 67% at 12 months. Nevertheless, further studies with more patients would help confirm this finding.

For imatinib in sclerotic GVHD, Olivieri et al. reported the efficacy of imatinib in a series of 19 patients with refractory GVHD and described significant improvement in skin fibrosis in half of the patients [30]. Similar observations were made by Magro et al., reporting that imatinib treatment for cGVHD could reduce skin sclerosis within two months of treatment start [31], with an ORR of 50%, including 28% of patients with CR and 71% with PR, and concluding that imatinib treatment could significantly reduce the daily corticosteroid dose. Baird et al. also reported that 36% of patients with sclerotic GVHD achieved PR with six months of imatinib treatment [45]. Similarly, the present study showed a 60% ORR at 12 months, with one patient (5%) achieving CR at six months, while 60% achieved a PR at 12 months. However, compared to ruxolitinib or imatinib, ibrutinib was not highly effective for sclerotic GVHD. Although Miklos et al. reported that Ibrutinib could significantly improve sclerotic GVHD in more than half of patients [26], this finding was not replicated in our study.

We acknowledge several limitations of the present study, including its retrospective nature with single-center data, a small sample size for each TKI group, and a relatively short duration of follow-up with limited access to individual organ response to the treatment. Despite its limited size, this cohort suggests the beneficial activity of TKIs in sclerotic cGVHD, warranting further prospective investigations.

In conclusion, based on our single-center experience, all three TKIs are feasible and effective for cGVHD treatment. Ruxolitinib seems superior to other TKI drugs for ORR, CB, FFS, and daily prednisone dose reduction. Ruxolitinib appears to be as effective as imatinib for sclerotic cGVHD in improving the PROM score of sclerotic GVHD.

Author contribution

S.M.L., O.A., and D.K. designed the study and collected and analyzed the data. S.M.L., I.N.B., and D.K. created the figures and wrote the manuscript. I.P., W.L., A.L., F.M., A.G., A.V., J.L., R.K., and J.M. provided valuable input into the study and reviewed and approved the manuscript. S.M.L. and I.N.B. contributed equally to this study and should be considered co-first authors.

Data availability statement

Data are available on request.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

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Appendix

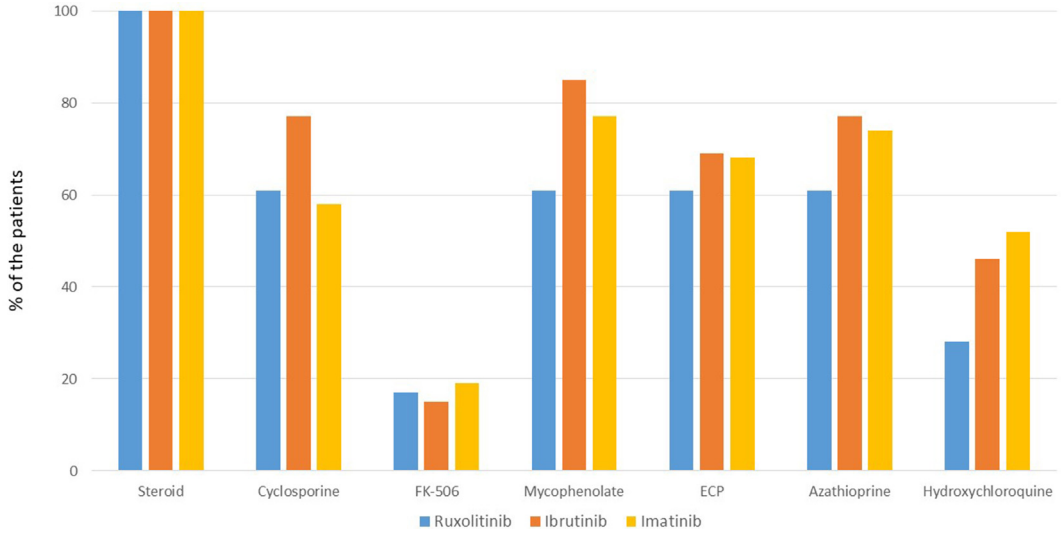

Fig. S1. Summary of the prior therapies for the chronic GHVD treatment.

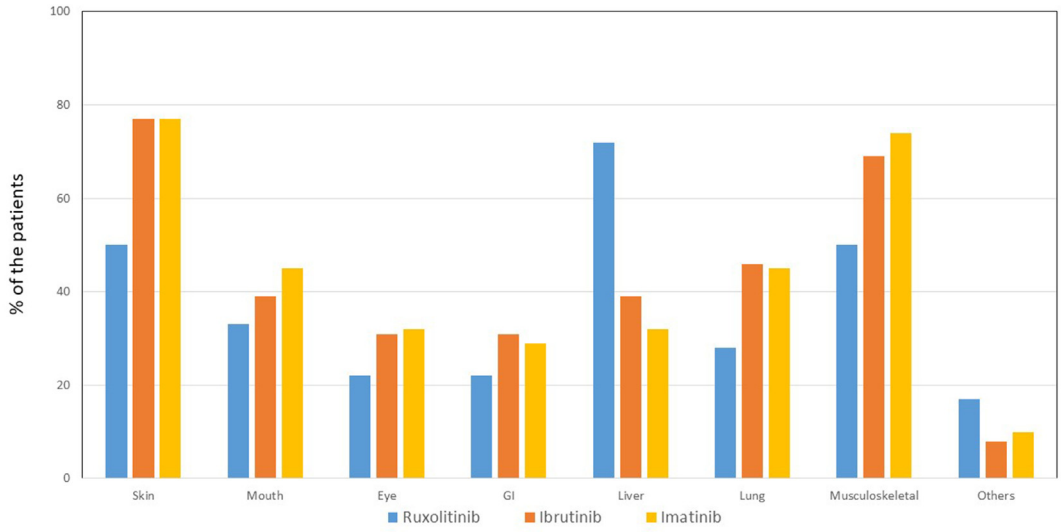

Fig. S2. Organ involvement at the time of TKI therapy starts.

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