ARTICLE

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Nilotinib efficacy and safety as salvage treatment following imatinib intolerance and/or inefficacy in steroid refractory chronic graft-versus-host-disease (SR-cGVHD): a prospective, multicenter, phase II study on behalf of the Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC)

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Imatinib is used for patients with SR-cGVHD. However, in 50% of cases imatinib is discontinued due to intolerance or inefficacy. In order to investigate nilotinib's role as salvage therapy in those patients, we conducted a prospective, multicenter, phase II study. (NCT02891395). Patients with SR-cGVHD were included to receive imatinib. Patients who stopped imatinib due to intolerance or inefficacy switched to Nilotinib. The primary endpoint was defined as the week-12 response rate to Nilotinib. The response was considered successful if superior to the 30% endpoint. Sixty-two patients started the IM-phase. Fourteen patients (22%) discontinued imatinib before week 12 due to: cGVHD progression (10%) or TKI-class-specific intolerance (12%). At week 12, we observed complete remission in 13 patients (21%) and partial response in 8 patients (13%). Twenty-nine patients switched to Nilotinib. Nilotinib response at week-12 was observed in 6 patients (21%) while 23 patients (79%) discontinued Nilotinib due to intolerance/cGVHD progression. The primary endpoint was not reached. This prospective study confirmed the efficacy of imatinib in patients with steroid refractory cGVHD. It failed to demonstrate the efficacy of nilotinib as a salvage therapy in patients who were intolerant/unresponsive to imatinib.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is a worldwide known procedure for acquired or congenital hematological and/or immunological disorders [1]. Chronic graft-versus-host disease (cGVHD) remains one of the most serious complications in long-term survivors. Despite many therapeutic advances over the last two decades, cGVHD incidence is increasing [2]. This rise is likely due to an increased use of matched unrelated donors, mismatched related donors, older age of recipients, and wider use of peripheral blood cells as a stem cell source [3–5].

Steroids are still the standard of treatment for cGVHD according to current guidelines [6, 7]. Unfortunately, approximately half of patients will fail first-line steroid treatment. On the other hand, a significant proportion will experience steroid dependency, with poor prognosis [8–10].

Nowadays, two kinase inhibitors, Ibrutinib and Ruxolitinib, are approved as a second line treatment of GVHD in many countries.

In case of intolerance to first- and second-line treatments or in settings of refractory GVHD, some tyrosine kinase inhibitors (TKIs) have been described and reported as potential salvage therapy. Imatinib mesylate (IM) is the best attractive example, especially as a dual inhibitor for modulating Transforming Growth Factor-β and platelet-derived growth factor receptor (PDGF-R) pathways, deeply implicated in both fibrogenic and inflammatory processes in cGVHD [11–13].

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We have already reported IM efficacy alone for refractory steroid sclerotic cGVHD (SR-cGVHD) [14] and in combination with extracorporeal photopheresis [15]. Second generation TKIs were also reported, in retrospective cohorts, as potential treatment for imatinib refractory and/or intolerant in sclerotic form of cGVHD [16, 17].

This two-step multicenter prospective study investigated the efficacy and safety of nilotinib (Nilo), a second generation TKI, as salvage treatment, in patients with SR-cGVHD who showed no response or intolerance to IM.

PATIENTS AND METHODS

Patients

Eligible patients were required to be ≥18 years old and <75 years old. Participants had to have undergone allo-HCT, despite conditioning regimen, from any hematopoietic stem cell source for any hematological disorder with a body weight >40 kg, with confirmed cGVHD, resistant to at least one systemic immunosuppressive therapy. The cGHVD diagnosis was based on the NIH Working Group Consensus [18]. Female patients of childbearing potential had to agree, before drugs initiation, to undergo efficient contraceptive precautions throughout the trial and for 3 months following the end of the trial's salvage phase.

Nine centers, as part of the Francophone Society of Bone Marrow Transplantation and Cell Therapy (SFGM-TC) participated in this study.

METHODS

Study design

This study, registered as: EudraCT 2012-000770-36 and NCT02891395, is an interventional, open label, non-randomized, multicenter, phase II trial with direct individual benefit. The efficacy and safety of Nilo, used as salvage therapy for patients with cGVHD who did not tolerate and/or were nonresponsive to IM induction phase, was studied. The primary objective was to investigate the efficacy of Nilo in cGVHD treatment in patients who did not respond/intolerant to IM. The primary endpoint was the response rate to Nilo by week 12 (for all patients under Nilo treatment, regardless the response status before week 12). The study was conducted in two phases: an induction phase (IM-phase) and a salvage phase (Nilo-phase).

All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki. Institutional review boards and independent ethics committees approved the protocol. Data were collected by the investigators and their teams.

Induction phase (IM-phase). IM was started at 100 mg/day and increased by 100 mg/day every 2 weeks up to the maximum tolerable dose with a threshold of 400 mg/day. For those responsive to treatment, and in the absence of toxicity, the treatment was maintained up to 1 year. As for patients who discontinued IM at week 12 due to lack of response (no response = stable disease), those who experienced progression at any time, those who relapsed after an initial response to IM at any time and those who discontinued IM for toxicity at any time, underwent the salvage phase.

Salvage phase (Nilo-Phase). Nilo was started at 200 mg/day and increased by 200 mg/day every 2 weeks up to maximum tolerable dose or 800 mg/day, whichever occurred first. In absence of toxicity, the treatment was maintained up to 1 year.

Statistical analyses

The primary endpoint was the proportion of patients achieving PR or CR with Nilo at week 12 and compared with the control history group (30%) using a one-sided Fisher exact. The two-sided 95% confidence interval (CI) was estimated using Clopper-Pearson method. Other efficacy endpoints included PR or CR with IM, overall survival (OS) and best response duration on IM and Nilo. Sample size calculation are detailed on the appendix 1

The proportion of patients with PR/CR over time was estimated with simple proportions (number of patients in PR or CR up to each time point divided by the total number of patients). OS and best response duration on IM and Nilo were estimated using Kaplan–Meier method. Follow-up duration was estimated by using reverse Kaplan–Meier method.

Data were analyzed using SAS software package, release 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics

IM-phase. Sixty-three patients (42 males/21 females) were included with a median age of 52 years at inclusion (Table 1). Patients were included after a median delay of 12.4 Months (0–131.3) from cGVHD diagnosis. All patients had refractory cGVHD with a median of 2 lines of prior therapy (range, 1–4), of whom 41% were included after one treatment line. Sixty-two eligible patients started the IM-phase between 27 December 2012 and 9 August 2016, while one patient dropped his consent 3 weeks after inclusion. Forty patients had a history of acute GVHD. All patients had resolved the acute GVHD before inclusion.

Fifty-one patients (81%) had chronic cutaneous GVHD of whom 43 patients (68%) had a sclerotic form of cGVHD. Active ocular cGVHD was recorded in 17 patients (27%), while hepatic involvement of cGVHD was recorded in 32 patients (50.5%). Digestive manifestations due to oral mucosis/gastrointestinal involvement varied between weight loss (18 patients, 30.5%), vomiting (4 patients, 6.8%) and solid elements swallowing difficulties (17 patients, 28.8%). Sleeping disorders were the predominant psychological manifestations with 34 patients (57.7%). Skin color changes and thickening were the most presented dermatological manifestations with 52 patients (88%) and 41 patients (69.4%), respectively. Pulmonary involvement was recorded in 34 patients (54%).

Median cGVHD Lee score was 25 points (2–66). Chronic GVHD was globally mild in 4 patients (6.8%), moderate in 21 (33%), severe in 38 (60%).

At inclusion time, median platelets and white blood cells were 237×10^9/L (48–574), 8.8 (2.6–20.8)/mm^3, respectively. Eight patients had a significant hypereosinophilia (≥1.5 G/l).

Table 1. Patient characteristics.

Patient characteristics		
	$n = 63$	Percentage
Male	42	67%
Female	21	33%
Age (median, range)	52 (18–70)	
Number of prior lines of treatment		
1	26	41%
2	17	27%
3	13	21%
4	7	11%
cGVHD severity		
Mild	4	7%
Moderate	21	33%
Severe	38	60%
Organ involved		
Skin	51	81%
Sclerodermous skin	43	68%
Mucous	44	70%
Ophtalmic	17	27%
Hepatic	32	50%
Pulmonary	34	54%
Gastrointestinal	3	5%
Number of organs involved		
1	18	29%
2	30	48%
3	13	20%
4	2	3%

Fourteen patients (22%) discontinued IM before week 12 because of cGVHD progression ($n = 6$, 10%) or TKI-class-specific intolerance ($n = 8$, 12%).

Nilo-phase. Twenty-nine patients (19 males/10 females) were included in phase 2. The median age was 51 years (range, 24–70, years). Patients were included after a median delay of 13.6 Months (0.1–52.9) from cGVHD diagnosis.

Twenty-six patients (90%) had chronic cutaneous GVHD of whom 18 patients (62%) had sclerotic form of cGVHD. Active ocular cGVHD was recorded in 10 patients (31%), while hepatic involvement of cGVHD was recorded in 14 patients (48%). Pulmonary involvement was presented in 16 patients (55%).

Chronic GVHD was globally mild in 1 patient (3.4%), moderate in 6 (20.7%), severe in 22 (75.9%).

At inclusion time, median platelets and white blood cells were 263×10^9/L (92–436), 7.8×10^9/L (1.7–19.2), respectively. Six patients had a significant hypereosinophilia (≥1.5 10^9/L).

Sixteen patients had history of acute GVHD. All patients resolved acute GVHD before inclusion.

The study flowcharts for both phases are available in Figs. 1 and 2.

Responses

IM-phase. Best response on IM was as follows: complete remission (CR) in 20 (32.8%), partial response (PR) in 11 patients (18%), stable disease (SD) in 28 patients (45.9%), 2 patients (3.3%) had always a

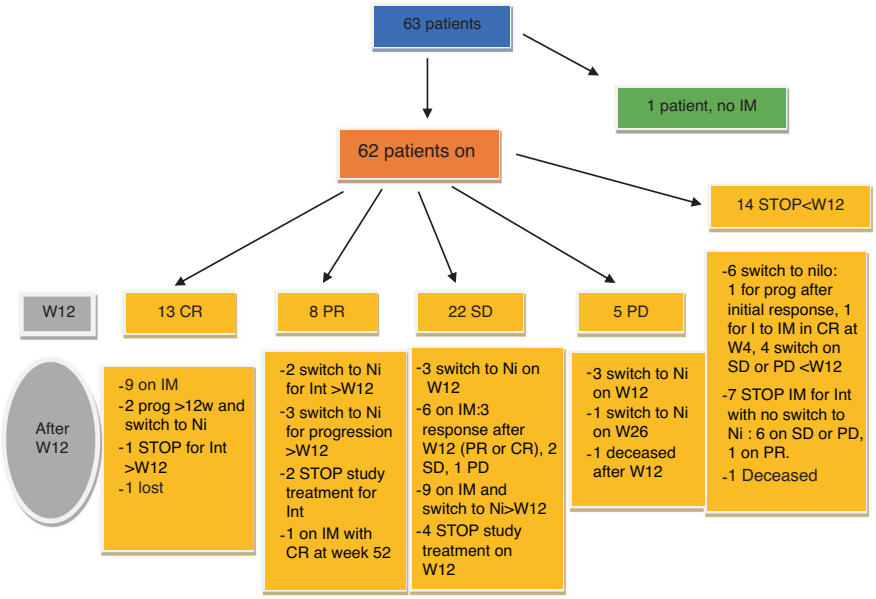

Fig. 1 Flowchart of the imatinib mesylate (IM) phase. It shows different subgroup according to response to IM at week 12. CR complete remission, PR partial remission, SD stable disease, PD progressive disease, prog progression, Ni nilotinib, W week, Int intolerance.

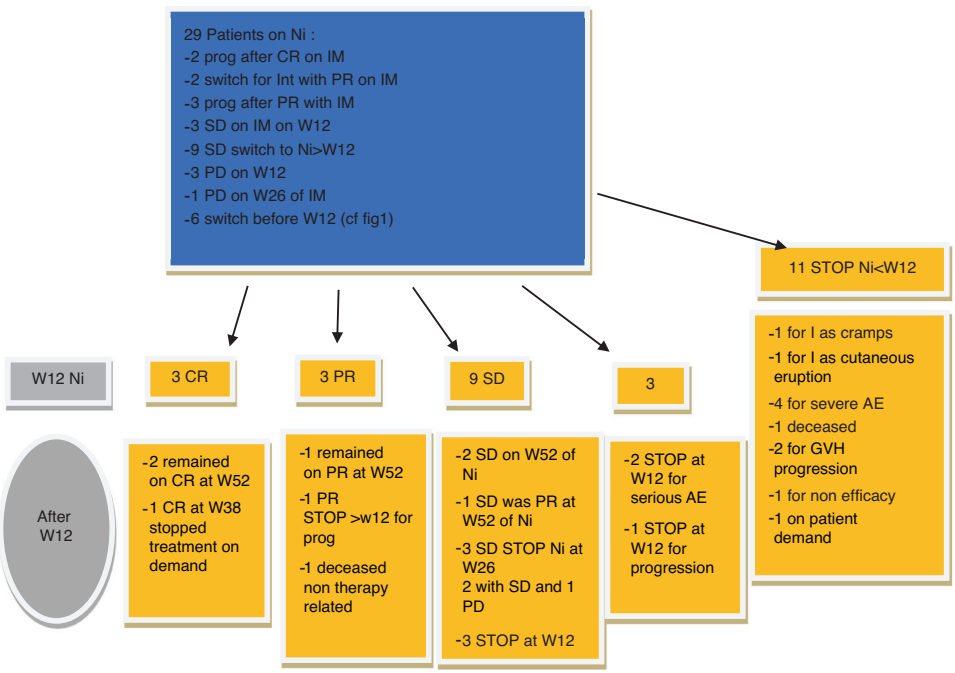

Fig. 2 Flowchart of the nilotinib (Ni) phase. It shows different subgroup according to response to Ni at week 12. CR complete remission, PR partial remission, SD stable disease, PD progressive disease, prog progression, Ni nilotinib, W week, Int intolerance.

Table 2. Response rate with IM and Ni regarding organ involvement (scld = sclerodermous, GI = gastrointestinal, Pulm = pulmonary).

	Skin	Scld skin	Mucous	Ophtalmic	Hepatic	Pulm	GI
IM (best response)	***N* = 51**	***N* = 43**	***N* = 43**	***N* = 16**	***N* = 31**	***N* = 33**	***N* = 3**
Complete	*15 (29.4)*	*11 (25.6)*	*15 (35.7)*	*5 (31.2)*	*11 (35.5)*	*10 (30.3)*	*0 (0.0)*
Partiel	9 (17.7)	8 (18.6)	8 (19.0)	3 (18.8)	6 (19.4)	5 (15.1)	1 (33.3)
Progression	*2 (3.9)*	*1 (2.3)*	*2 (4.8)*	*0 (0.0)*	*1 (3.2)*	*2 (6.1)*	*0 (0.0)*
Stable	25 (49.0)	23 (53.5)	17 (40.5)	8 (50.0)	13 (41.9)	16 (48.5)	2 (66.7)
missing	*0*	*0*	*0*	*0*	*0*	*1*	*0*
Nilo (response at W 12)	***N* = 26**	***N* = 26**	***N* = 20**	***N* = 9**	***N* = 14**	***N* = 16**	***N* = 2**
Complete	*2 (7.7)*	*2 (7.7)*	*3 (15.0)*	*0 (0.0)*	*1 (7.1)*	*1 (6.2)*	*0 (0.0)*
Partiel	2 (7.7)	2 (7.7)	1 (5.0)	0 (0.0)	1 (7.1)	2 (12.5)	0 (0.0)
Progression	*3 (11.5)*	*3 (11.5)*	*2 (10.0)*	*1 (11.1)*	*1 (7.1)*	*2 (12.5)*	*0 (0.0)*
Stable	9 (34.6)	9 (34.6)	*7 (35.0)*	4 (44.4)	3 (21.4)	4 (25.0)	2 (100)
Discontinued Nilo before W12	*(10 38.5)*	*10 (38.5)*	*7 (35.0)*	*4 (44.4)*	*8 (57.1)*	*7 (43.8)*	0 (0.0)

Table 3. Response rate with IM and Ni regarding number of prior line treatment (1–2 versus 3–4).

	Prior lines of treatment		
	1–2	**3–4**	***P* Value[a]**
IM (best response)	*N* = 42	*N* = 20	
Complete	16 (38.1)	4 (21.1)	0.42
Partiel	7 (16.7)	4 (21.1)	
Progression	2 (4.8)	0 (0.0)	
Stable	17 (40.5)	11 (57.9)	
missing		*1*	
Nilo (response at week 12)	***N* = 19**	***N* = 10**	
Complete	3 (15.8)	0 (0.0)	0.63
Partiel	2 (10.5)	1 (10.0)	
Progression	2 (10.5)	1 (10.0)	
Stable	5 (26.3)	4 (40.0)	
Discontinued Nilo beforeW12	*7 (36.8)*	*4 (40.0)*	

[a]*P* Value (Fisher 's exact test) for comparison in the response rate (complete/partial).

progressive disease (PD) while one patient had a non-evaluable/unvalidated response.

At week 12, 54 patients completed the EORTC-QLQ-C30 form (details on appendix 1), with a mean and median score 50.0 (±15.2) and 45 (30–92) respectively. Twenty-one patients (34.4%, 95% CI, 22.7–47) were responsive with CR ($n = 13$, 21%), and PR ($n = 8$, 13%), while 22 (35%) had stable cGVHD and 5 (8%) had a progressive cGVHD, as shown in the flowshart in Fig. 1.

From those responders, 16/21 had initial cutaneous cGVHD, 7/21 had ophthalmic involvement and 11/21 had pulmonary affection (details regarding organ involvement response are shown in Table 2).

Nilo-phase. Twelve non-responders patients switched to Nilo before or at week 12 according to protocol design. Additional 17 patients switched to Nilo later, because of progression or intolerance to imatinib. Fourteen patients with different types of response (23%) remained on IM till the end of the study.

Seven patients experienced intolerable treatment-related adverse events that lead eventually to treatment interruption.

Among the 29 patients who started the Nilo phase, response at week 12 was observed in 6 patients (20.7%) while 23 patients (79.3%) discontinued Nilo for intolerance or progression of the cGVHD, as shown in Fig. 2. With this response rate, the primary endpoint was not reached (one-sided p value = 0.81 for comparison with 30% as minimal efficacy criteria) and the salvage-phase with Nilo was considered as failure.

Beside one patient on PR, all the other 5 responders didn't respond initially to IM. 3 patients over 6 did pursue Nilo at an optimal dose of 600 mg/day for almost a year (range 229–356 days), and three patients had a dose reduction for toxicity at 10, 16 and 32 days after initiation.

More details on response rate according organ involvement and different prior line treatment are shown on Tables 2 and 3.

Overall survival is shown in Fig. 3, while the duration of the best response according to best response following IM and Ni are shown in Figs. 4 and 5.

Safety profile. Four patients deceased within the 1-year scheduled follow-up, as shown in the two flowcharts in Figs. 1 and 2. Only one patient was on Nilo, the other three patients were not. They had all progressive cGVHD.

Two patients deceased from causes unrelated to the study treatment of the cGVHD, two other patients deceased while having grade ≥3 treatment-related adverse events.

Six patients stopped Nilo treatment due to secondary effects: one for muscular cramps; one for cutaneous toxicity; one for abnormal ECG findings. The other three experienced a variety of symptoms: paresthesia; edemas; neutropenia; fatigue.

DISCUSSION

Our results show prospectively a good, best response rate on IM treatment (CR 32.8%, PR 18%), where more than half of patients responded favorably to this therapeutic approach.

These results are in accordance with other published data showing that IM may be a valid treatment option for some refractory cGVHD patients, especially those who don't respond to first and second line [14, 19].

The mechanism behind IM efficacy, is related to its multi-target tyrosine kinase inhibition [20], on PDGFR, that is implicated in fibroblast chronic activation [21–23].

It seems that PDGFRs are implicated in various Inflammatory states (fibroid-inflammatory and tumoral-inflammatory disease) [24]. In murine models, IM has also shown to be effective in PDGFR inhibition in different aspects such as sclerodermatous cutaneous cGVHD. This is the most likely mechanism of action behind the encouraging clinical results of imatinib in SR-cGVHD [14, 25]. We, once again, confirm these results in our prospective study, during the initial phase.

Nilo is a second generation TKI that was designed based on the molecular structure of Imatinib with a better topographical fit for the ABL protein [26].

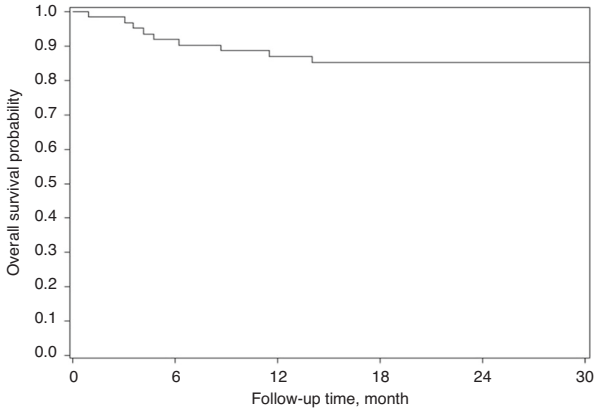

Fig. 3 Overall survival. It shows patient's overall survival during the trial.

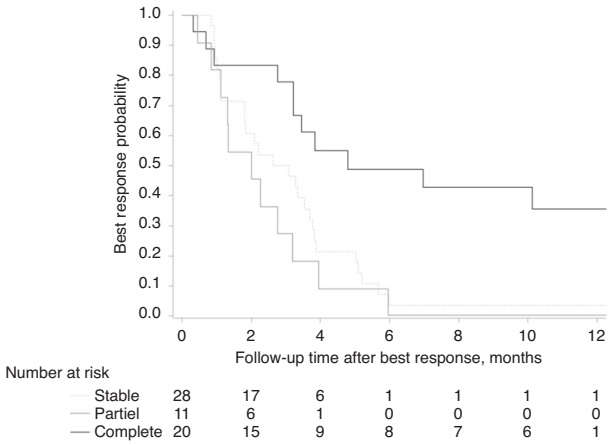

Fig. 4 Best response duration in the imatinib mesylate group. Duration of the best response according to best response following imatinib mesylate.

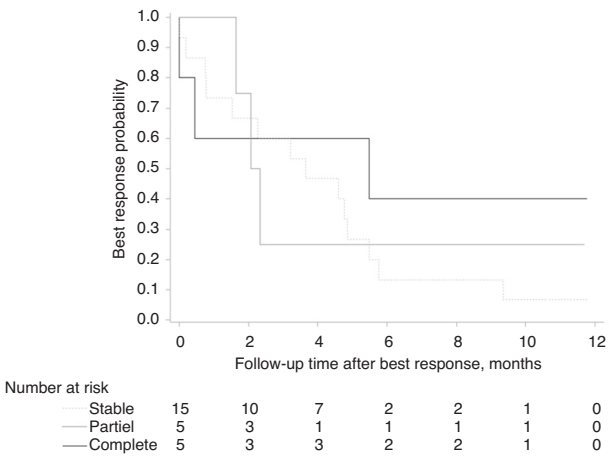

Fig. 5 Best response duration in the nilotinib group. Duration of the best response according to best response following nilotinib.

During the study, we observed a response rate of almost 21% on Nilo at week 12. However, we noticed a loss of IM response in 7 patients who switched to Ni salvage treatment. None of these 7 patients responded to Ni, suggesting probably a similar mechanism of resistance to Ni as for IM. Details on response rate on Ni according to the first IM response are detailed on Table 4.

Table 4. Response rate to Ni according to the reason for switch to Ni.

		Response to Ni at W12
Patient on salvage phase	$N = 29$	6
Loss of IM response	$N = 7$	0
Intolerance to IM	$N = 3$	1
No response to IM	$N = 19$	5

Though, it was previously shown that TKIs have inhibitory effects on immunologic reconstitution and T cell function and proliferation [27, 28]. This active immune regulation could be suggested as a potential mechanism of TKI of action in cGVHD by restoring the imbalance between Treg and effector T cells [29–31]. As for Nilo, the same mechanism on Treg cells and CD4 + CD25-effector T cells has been noticed, but only with concentration greater than standard dose used on daily base for CML treatment [32–34]. Considering these facts, we first suggest that the previous exposure to IM, did already restore T cell reconstitution and function imbalance (especially on those who responded first on IM), resulting in the less response rate in our study when compared to the GITMO study group [19] where *Olivieri et al*. showed an ORR at 6 months of almost 28% on Nilo when used as a first TKI in SR cGVHD with almost no previous exposure to IM (only 2 patients of 21 had IM).

Regarding steroid usage, we noticed 57 patients were treated with corticosteroid at IM initiation (data not shown). As for the timing to Ni initiation, 26 patients were on steroid. These results can be explained by the fact that most of patients were switched to Ni because of progression or on SD on IM.

On the other hand, we also suggest that Nilo dosage might be important. At least half of the responders were at the dose of 600 mg/day and above while in the non-responder group only 7 out of 23 had doses superior or equal to 600 mg/day at week 12 after Nilo initiation. Van der wagen et al. did suggest this plausible explanation when comparing their results (Nilo in SR-cGVHD monotherapy after rituximab induction) to those by Chen et al. [35, 36].

Limitations

First, the goal number of participants for Nilotinib phase was not reached, which can be explained by the higher-than–expected response rate during the imatinib phase. So, the statistical power is calculated at 64%.

The timing of Ni efficacy evaluation at week 12 may also be discussed in this context. Since Ni has a higher intolerance profile, especially after allo-HCT, we observed a higher response rate before week 12, with a best response rate of 26%. Though a better delay could be fixed but with no solid available data in the literature.

In our study, we did not perform serum level dosage of TKIs, thus we notice a response rate of 30% in the group of Nilo 600 mg, and only 15.7% on the Nilo <600 mg.

Finally, in the study design, limited items were collected concerning the pre-GVHD phase.

CONCLUSION

This prospective phase II study for Nilo as a salvage treatment for refractory/intolerant to imatinib in SR-cGVHD did not show a significant improvement. This lack of evidence is probably due to the previous exposure to imatinib resulting in greater TKI resistance and a decreased immunomodulatory effect of Nilo. Though, we do not encourage the use of Nilo after IM exposure. Nevertheless, we confirm in this prospective analysis the clinical benefit of imatinib in SR-cGVHD. Further research is needed, especially with Nilotinib as front line TKI inhibitor in SR-cGVHD, with a comparison IM versus Nilo.

DATA AVAILABILITY

The dataset generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

IYA, LM, TA, and MS have contributed to the project conceptualization. TA and MS have contributed equally to this paper preparation and drafting. IYA have supervised the project and contributed to the finalization of the paper. JL have accomplished the statistical analysis. All authors read and approved the final draft.

COMPETING INTERESTS

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