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ORIGINAL ARTICLE

Ruxolitinib in the management of steroid-resistant/-dependent acute and chronic graft-versus-host disease: results of routine practice in an academic centre

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Abstract

Graft-versus-host disease (GVHD) is an important complication after allogeneic haematopoietic stem cell transplantation (HSCT). Corticosteroids are the standard first-line treatment. Steroid-resistant/-dependent (SR/D) acute and chronic GVHD (aGVHD, cGVHD) lead to significant morbidity/mortality. The JAK2 inhibitor ruxolitinib has recently been shown in clinical trials to be effective in SR/D aGVHD and cGVHD. We retrospectively analysed the efficacy and safety of ruxolitinib in a cohort of SR/D aGVHD and cGVHD patients treated in a non-trial setting. In the aGVHD cohort, there were 14 men and 12 women, median age at 38 (19–63) years. At day 28 post-ruxolitinib, the overall response rate (ORR) was 86% (complete response, CR, 36%; partial response, PR, 50%). Continued ruxolitinib beyond day 28 resulted in a final CR of 68%. However, 3/15 (20%) of CR patients developed cGVHD. In the cGVHD cohort, there were 16 men and 15 women, median age at 33 (21–64) years. The ORR, CR and PR rates changed with continued ruxolitinib treatment, being 86%, 17% and 69% at 1 month; 79%, 38% and 41% at 3 months; and 83%, 52% and 31% at 6 months. Five patients had overlap GVHD, four of whom achieved CR. Multivariate analysis showed that superior overall survival and failure-free survival were associated with CR at day 28 for aGVHD, and CR at 1 year for cGVHD. Ruxolitinib treatment was efficacious for SR/D aGVHD and cGVHD, and continued treatment for at least 6 months was needed to maximize benefit.

Keywords Graft-versus-host disease · Chronic · Acute · Steroid-refractory/-dependent · Ruxolitinib

Introduction

Graft-versus-host disease (GVHD) is an important complication of allogeneic haematopoietic stem cell transplantation (allo-HSCT), which results in significant morbidity and is the main cause of non-relapse mortality. The traditional division at day 100 into acute and chronic GVHD (aGVHD, cGVHD) [1, 2] has been modified to accommodate late acute GVHD and overlap chronic GVHD [3].

Treatment of aGVHD depends on high-dose corticosteroids [1]. In patients who develop steroid-resistant aGVHD (SR-aGVHD), various conventional immunosuppressive therapies have been used, with no obvious advantages of one agent over another [1]. However, the JAK inhibitor ruxolitinib has been shown in a randomized trial to result in significantly superior response rates than best available therapy (BAT) in patients with SR-aGVHD [4].

The management of cGVHD is more complicated, because it is a chronic process that may last years, resulting in significant tissue/organ damage that may be irreversible. Corticosteroids are the standard first-line treatment. For steroid-resistant or steroid-dependent (SR/D) patients, second-line immunosuppressive therapy (IST) comprising calcineurin inhibitors, rituximab, mycophenolate mofetil and mTOR inhibitors, together with extracorporeal photopheresis and the Bruton tyrosine kinase inhibitor ibrutinib, are predominantly employed [5]. Recently, similar to SR-aGVHD, ruxolitinib has been shown to result in significantly superior response rates than BAT in patients with SR/D-cGVHD [6].

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Previous published studies of ruxolitinib in aGVHD and cGVHD were predominantly retrospective multicentre analyses [7–19]. The majority of these studies were on patients with SR-aGVHD, but SR/D-cGVHD had also been included. These studies generally showed that ruxolitinib was effective. However, an accurate assessment of the efficacy of ruxolitinib was confounded by the multicentre nature of most of these studies, which led to differences in patient selection, timing of ruxolitinib use, response criteria and duration of follow-up.

In this study, we conducted a single-centre retrospective analysis of a cohort of patients with aGVHD and cGVHD, who received ruxolitinib predominantly as salvage therapy, and were assessed by uniform sets of published response criteria.

Materials and methods

Patients

The prescription records from January 1, 2015, to December 31, 2019, of consecutive allo-HSCT patients who received ruxolitinib for treatment of aGVHD/cGVHD were identified and reviewed. Definitions of aGVHD and cGVHD were adopted from previous published criteria [3]. Data collected included demographics, underlying diseases, response rates and adverse events. Patients gave informed consent for treatment, and institute review board approval was obtained for this retrospective study.

HSCT protocols and GVHD prophylaxis

Myeloablative conditioning was used for patients ≤ 55 years old, with adequate organ function and no significant comorbidities, and undergoing first HSCT. For patients with significant comorbidities, inadequate organ function, having received ≥ 1 previous HSCT, or age > 55 years; reduced intensity conditioning (RIC) was used. Haplo-identical HSCT had a separate conditioning (Supplemental file 1). GVHD prophylaxis was methotrexate (MTX) + cyclosporine A (CsA) for sibling HSCT, MTX + CsA + mycophenolate mofetil (MMF) for voluntary-unrelated-donor (VUD) HSCT, and CsA + MMF + post-transplantation cyclophosphamide (PTCy) for haplo-identical HSCT (Supplemental file 1).

Evaluation of aGVHD and cGVHD

For aGVHD, classification into classical (within first 100 days), late-onset (> 100 days), recurrent and persistent subtypes and staging of involved organs and grading were performed according to published criteria [20]. For cGVHD, classification into classical (onset > 100 days) and overlap (concurrent aGVHD and cGVHD) subtypes [21, 22] and organ evaluation and grading, including the scoring of organ-specific severity (0–3) and global severity (mild, moderate, severe), were performed according to the NIH criteria [3, 21].

Treatment

For aGVHD, standard treatment comprised intravenous methylprednisolone (2 mg/kg/day). SR-aGVHD was defined according to standard criteria [4]. Patients could not achieve at least partial response after 7 days of treatment or failed tapering of methylprednisolone to < 0.5 mg/kg/day for a minimum of 7 days. For cGVHD, standard initial treatment comprised oral prednisolone at 1 mg/kg/day. SR/D-cGVHD was defined according to standard criteria [20]. Patients had a lack of response or disease progression after at least 1 week of treatment, or disease persistence without improvement with prednisolone used at > 0.5 mg/kg/day for 4 weeks, or two or more unsuccessful attempts to taper prednisolone to < 0.25 mg/kg/day. In patients who failed steroid tapering, manifesting as disease flare during dose reduction, ruxolitinib was administered to achieve a response so that steroids might be gradually withdrawn without disease deterioration. No additional immunosuppressants were used together with ruxolitinib in such cases. Similarly, in selected cases ruxolitinib was used to enable tapering of other immunosuppressants. Ruxolitinib was initiated at a dose of 5 mg twice daily and escalated to 10 mg twice daily. When objective responses were obtained, tapering off of immunosuppressants followed the order of CsA, MMF and ruxolitinib.

Assessment of response and safety

Response of aGVHD was evaluated according to published criteria [7]. Complete response (CR) was defined as resolution of all symptoms and manifestations of aGVHD. Partial response (PR) was defined as improvement by one or more stage of aGVHD in one or more organs, without deterioration in other organs. Non-response (NR) was defined as no improvement, deterioration by at least one stage in any organ, involvement of previously unaffected organs, or necessity of additional drugs. Response of cGVHD was evaluated according to the NIH criteria [22]. CR was defined as resolution of all manifestations in involved sites or organs. PR was defined as improvement in at least one organ or site without deterioration in other organs or sites. NR was defined as no improvement, mixed response, or disease deterioration. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [23].

Table 1 Demographic and clinicopathological features of 62 patients with acute and chronic graft-versus-host disease treated with ruxolitinib

Parameters	Graft-versus-host disease		
	Acute ($N=26$)	Chronic ($N=31$)	Overlap ($N=5$)
Sex			
Male	14 (54%)	16 (51%)	2 (40%)
Female	12 (46%)	15 (49%)	3 (60%)
Median age (range), years	38 (19–63)	33 (21–64)	31 (23–57)
Primary haematological disease			
Acute myeloid leukaemia	12 (46%)	13 (42%)	1 (20%)
Acute lymphoblastic leukaemia	9 (35%)	7 (23%)	3 (60%)
Myelodysplastic syndrome/myeloproliferative neoplasm	2 (8%)	9 (29%)	1 (20%)
Non-Hodgkin lymphoma	2 (8%)	2 (6%)	0
Aplastic anaemia	1 (4%)	0	0
Status at haematopoietic stem cell transplantation			
First complete remission	13 (50%)	21 (68%)	4 (80%)
Second complete remission	6 (23%)	7 (23%)	0
Third complete remission	2 (8%)	1 (3%)	1 (20%)
Second relapse	2 (8%)	0	0
Stable disease	3 (12%)	2 (6%)	0
Haematopoietic stem cell transplantation			
First	22 (85%)	24 (77%)	4 (67%)
Second	3 (12%)	7 (23%)	2 (33%)
Third	1 (4%)	0	0
Donor			
Voluntary unrelated[A]	19 (73%)	19 (61%)	3 (60%)
Sibling[B]	4 (15%)	10 (32%)	1 (20%)
Haplo-identical	3 (12%)	2 (6%)	1 (20%)
HLA-loci mismatch			
0	12 (46%)	23 (74%)	3 (60%)
1	8 (31%)	6 (19%)	1 (20%)
>1	6 (23%)	2 (6%)	1 (20%)
Source of haematopoietic stem cells			
Peripheral blood	19 (73%)	26 (84%)	5 (100%)
Bone marrow	7 (27%)	4 (13%)	0
Peripheral blood + bone marrow	0	1 (3%)	0
Conditioning			
Myeloablative	17 (65%)	19 (61%)	4 (80%)
Reduced-intensity	9 (35%)	11 (35%)	1 (20%)
Donor lymphocyte infusion	0	1 (3%)	0

A: matched at 8 loci (A, B, C, DRB1); B: matched at 6 loci (A, B, DRB1)

Survivals

Overall survival (OS) was defined as the time from first dose of ruxolitinib to death (event) or last follow-up (censor). Failure-free survival (FFS) was defined as the time from first dose of ruxolitinib to disease relapse, progression or new manifestations of existing GVHD, development of cGVHD (in aGVHD patients), need of new or additional systemic medication for GVHD, death (events) or last follow-up (censor). Probability of complete tapering of IST was defined as the proportion of patients in whom IST could be successfully stopped without active GVHD. Analysis of survivals (OS, FFS) and probability of complete tapering of IST was conducted using the Kaplan–Meier method. The impacts of sex; prior HSCT (0 *versus* ≥ 1); conditioning regimens (myeloablative *versus* RIC); donor type (sibling *versus* VUD *versus* haplo-identical); HLA matching (matched *versus* mismatch of ≥ 1 HLA); source of HSC (bone marrow

Table 2 Clinicopathological features and response of steroid-refractory/-dependent acute graft-versus-host disease (aGVHD) to ruxolitinib

Parameters	Numbers (total = 22)
Types of aGVHD	
Classic	16 (73%)
Late onset	4 (18%)
Recurrent	2 (9%)
Severity of aGVHD	
Grade 1	0 (0%)
Grade 2	13 (59%)
Grade 3	4 (18%)
Grade 4	5 (23%)
Indications of treatment	
Steroid-refractoriness	14 (64%)
Steroid-dependence	8 (36%)
Concurrent immunosuppressive therapy	
Cyclosporine	22 (100%)
Mycophenolate mofetil	18 (82%)
Others	2 (9%)
Prior lines of aGVHD treatment	
1	8 (36%)
2	12 (55%)
≥ 3	2 (9%)
Daily total dose of ruxolitinib	
5 mg	2 (9%)
10 mg	14 (64%)
20 mg	6 (27%)
Responses at day 28	
Complete response	8 (36%)
Partial response	11 (50%)
No response	3 (14%)

versus peripheral blood *versus* bone marrow + peripheral blood), severity of GVHD (aGVHD: grade 1–2 *versus* 3–4; cGVHD: mild/moderate *versus* severe); prior lines of GVHD treatment (1 *versus* > 1), total daily treatment dose of ruxolitinib (≤ 10 mg *versus* 20 mg); and response after ruxolitinib (CR *versus* PR *versus* NR) on survivals were analysed by univariate and multivariate analysis using Cox regression with the forward stepwise method. Two-tailed *P* values of < 0.05 were considered as significant. All tests were performed with the SPSS 21.0 software package.

Results

Patients with aGVHD

The cohort comprised 14 men and 12 women at a median age of 38 (19–63) years (Table 1). The majority of patients underwent HSCT from VUD (19/26, 73%), with ≥ 1 HLA-mismatch (14/26, 54%) and peripheral blood HSC grafts (19/26, 73%).

Patterns of aGVHD

Classical aGVHD was most frequent (65%), followed by late-onset (23%) and recurrent (12%) subtypes (Table 2, Supplemental file 2). The median time of onset of aGVHD was 70 (9–767) days post-HSCT (data shown in supplemental file 2, with three cases of late-onset aGVHD occurring at days 203, 411 and 767). Skin was the main organ affected (77%; stage 2–4: 80%), followed by the gastrointestinal tract (46%; stage 2–4: 75%). All patients had grades ≥ 2 aGVHD, with 35% having severe (grade 3–4) disease (supplemental file 2).

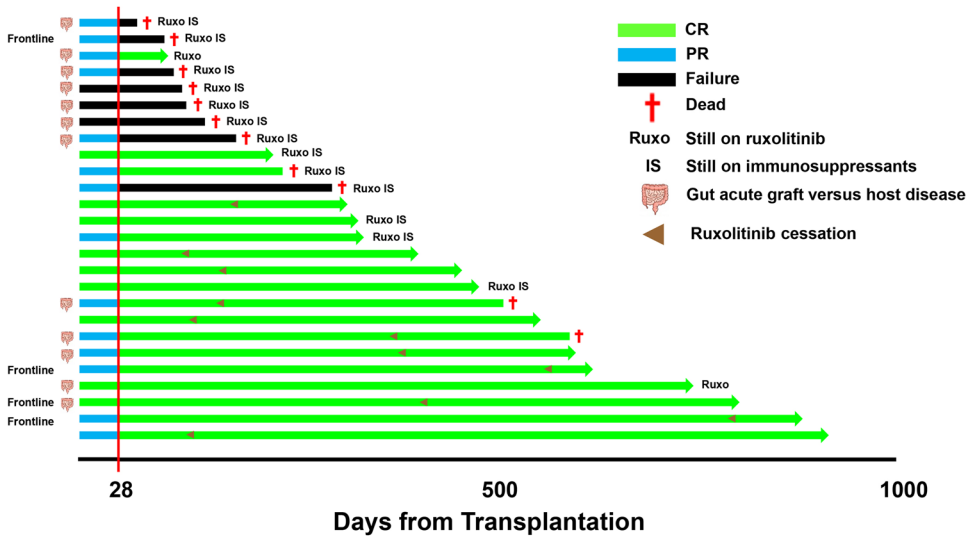

Fig. 1 Swimmer plot of patients with acute graft-versus-host disease treated with ruxolitinib

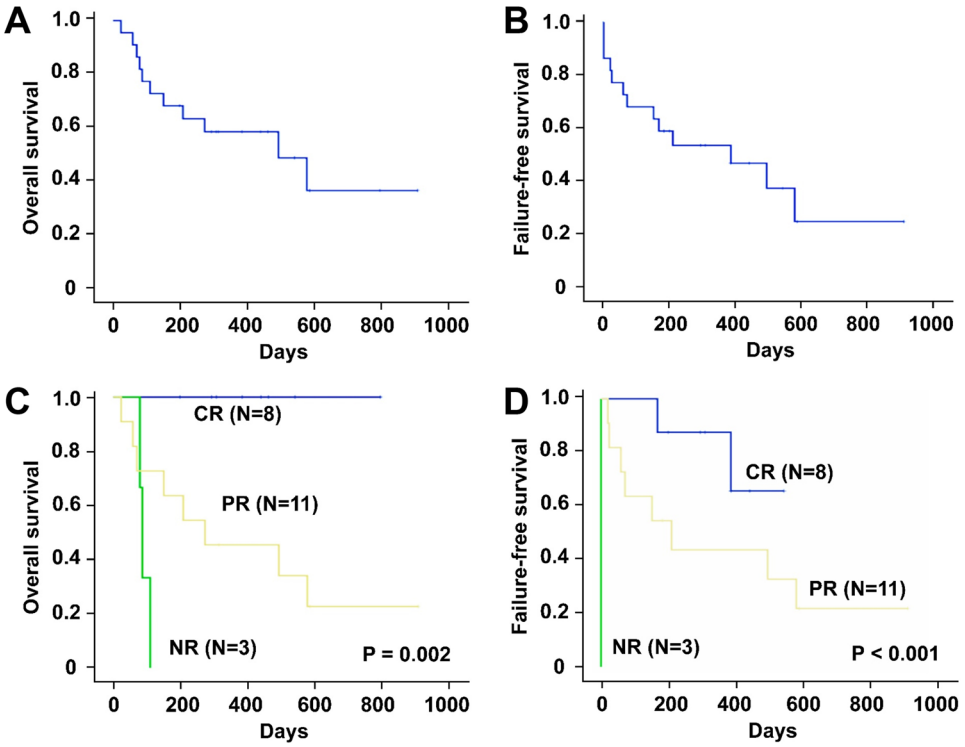

Fig. 2 Survival curves of patients with acute graft-versus-host disease treated with ruxolitinib. CR: complete response; PR: partial response; NR: no response

Treatment and outcome

SR/D-aGVHD was the main indication of treatment (85%), although four patients (15%) received ruxolitinib (with concomitant corticosteroid) as first-line therapy (at the discretion of attending physicians) (Fig. 1). As these frontline cases were few and could affect the evaluation of response rates and survivals of SR/D-aGVHD cases, they were only indicated in Fig. 1 and excluded from subsequent analyses (Table 2). At day 28 post-ruxolitinib, for the 22 SR/D-aGVHD patients, the overall response rate (ORR) was 86% (CR, 36%; PR, 50%) (Fig. 1, Table 2). Beyond day 28, all CR patients maintained their response. In the 11 PR cases, continued ruxolitinib treatment upgraded the response to CR in 7 patients, so that the CR rate finally increased to 68% (15/22) at 3 months. Four PR patients lost their response. None of the NR patients responded beyond 28 days. Three of 15 CR patients (20%) developed cGVHD involving liver ($N=1$) and skin ($N=2$) after 6–13 months of continued ruxolitinib treatment. The patient with liver cGVHD was able to achieve CR and ruxolitinib was stopped. The other two patients were maintained on ruxolitinib. At a median follow-up of 13 (4–30) months, 8 of 15 CR patients had complete tapering of all IST and were taken off ruxolitinib, with 6 of these occurring before day 300, and two before day 500. Two patients had complete tapering of IST and required only ruxolitinib treatment, whereas four patients were still on IST and ruxolitinib (Fig. 1).

Survivals

The OS and FFS of the aGVHD cohort were shown in Fig. 2. The 1-year and 2-year OS were 58% and 37%, and the 1-year and 2-year FFS were 54% and 25%. Superior OS was associated with myeloablative conditioning ($P=0.011$), grade I/II aGVHD ($P=0.005$) and CR at day 28 ($P=0.002$); and superior FFS was associated with CR at day 28 ($P<0.001$) (Fig. 2) (Supplemental file 3). Multivariate analysis showed that the only significant factor impacting on OS and FFS was response at day 28 (Fig. 2).

Patients with classical cGVHD

The cohort comprised 16 men and 15 women at a median age of 33 (21–64) years (Table 1). HSCT from VUD was most common (19/31, 61%), with a predominance of peripheral blood HSC grafts (26/31, 84%).

Patterns of classical cGVHD

The median number of organs involved was 1 (1–4), with mouth (61%), liver (45%), skin (32%) and eyes (32%) the most common sites affected (Table 3). Overall, 74% of patients had moderate to severe cGVHD.

Table 3 Clinicopathological features and response of chronic graft versus host disease (cGVHD) to ruxolitinib

Parameters	Numbers (total = 29)
Organs involved	
Mouth	19 (66%)
Liver	14 (48%)
Skin	10 (35%)
Eye	9 (31%)
Joints and fascia	3 (10%)
Lungs	2 (7%)
Gastrointestinal tract	1 (3%)
Overall severity (National Institute of Health classification)	
Mild	7 (24%)
Moderate	15 (52%)
Severe	7 (24%)
Indications of treatment	
Steroid-refractory/sparing	20 (65%)
Other immunosuppressants-sparing	9 (29%)
Concurrent immunosuppressive therapy	
Steroid	18 (62%)
Cyclosporine	26 (90%)
Mycophenolate mofetil	26 (90%)
Sirolimus	7 (24%)
Thalidomide	4 (14%)
Prior lines of cGVHD treatment	
1	2 (7%)
2	12 (41%)
≥ 3	15 (52%)
Total daily dose of ruxolitinib	
5 mg	3 (10%)
10 mg	21 (72%)
20 mg	5 (17%)
Responses after 1/6/12 months	
Complete response	5 (17%)/15 (56%)/14 (61%)
Partial response	20 (69%)/9 (33%)/7 (30%)
No response/loss of response	4 (14%)/3 (11%)/2 (9%)

Treatment and outcome

The indications of ruxolitinib treatment were steroid-refractoriness/sparing ($N = 20$; 65%), sparing of other IST ($N = 9$; 29%) and upfront use ($N = 2$; 6%). As the frontline cases were few and could affect the evaluation of response rates and survivals of SR/D-cGVHD cases, they were excluded from subsequent analyses (Table 3). In this cohort, there were seven patients with mild cGVHD. The indication for treatment was liver involvement. They had normal bilirubin levels, with progressive increase of alanine aminotransferase exceeding 3–5 times the upper reference value, so that ruxolitinib treatment was administered to halt further deterioration. One patient also had skin, mouth and eye involvement not responding to topical treatment, thus necessitating systemic therapy. Assessment of responses at 1, 3 and 6 months showed stable ORRs at around 70% (Fig. 3A and B). However, there was a progressive upgrade of PR to CR. The ORR, CR and PR rates were, respectively, 86%, 17% and 69% at 1 month; 79%, 38% and 41% at 3 months; and 83%, 52% and 31% at 6 months (Fig. 3B, C). From 6 months onwards, CR patients still maintained their responses, but more than half of the PR patients lost their responses (Fig. 3C). In responding patients, the probability of complete tapering of ISTs at 1 and 2 years were 25% and 44% (Fig. 3D). When ruxolitinib was used in patients who failed steroid tapering, prednisolone could be weaned off in 29% (2/7) of cases at 30 days and 71% (5/7) of cases at 60 days.

Survivals

The OS and FFS of the cGVHD cohort were shown in Fig. 4. At a median follow-up of 19 (1–41) months, the 1-year and 2-year OS were 94% and 81%, and the 1-year and 2-year FFS were 68% and 63%. Univariate analysis showed that the only significant prognostic indicator was CR within 12 months of ruxolitinib initiation, which was associated with superior OS ($P = 0.012$) and FFS ($P = 0.013$) (Fig. 4) (Supplemental file 4).

Patients with overlap GVHD

Five patients had overlap chronic GVHD. Acute manifestations included gastrointestinal (diarrhoea) in three patients and dermatologic (rashes) in two patients, associated with other symptoms of cGVHD. They were initially treated with corticosteroids, became steroid-refractory/-dependent, and received ruxolitinib as salvage. Four patients responded and achieved CR. One patient (with acute gastrointestinal manifestations) did not respond and had multiple recurrences on tapering of glucocorticoids and other immunosuppressants, dying 22 months after initiation of ruxolitinib. In the four responding patients, complete tapering of ruxolitinib resulted in recurrence of hepatic cGVHD in one patient, who achieved CR again after re-treatment with ruxolitinib.

Safety

Adverse events are shown in supplemental file 5. Most observed grade 1–2 adverse events were cytopenia followed by viral infections/reactivations. Severe infections occurred in 13% of the patients and most of them (7/8) occurred in patients with acute GVHD receiving large doses of immunosuppressants.

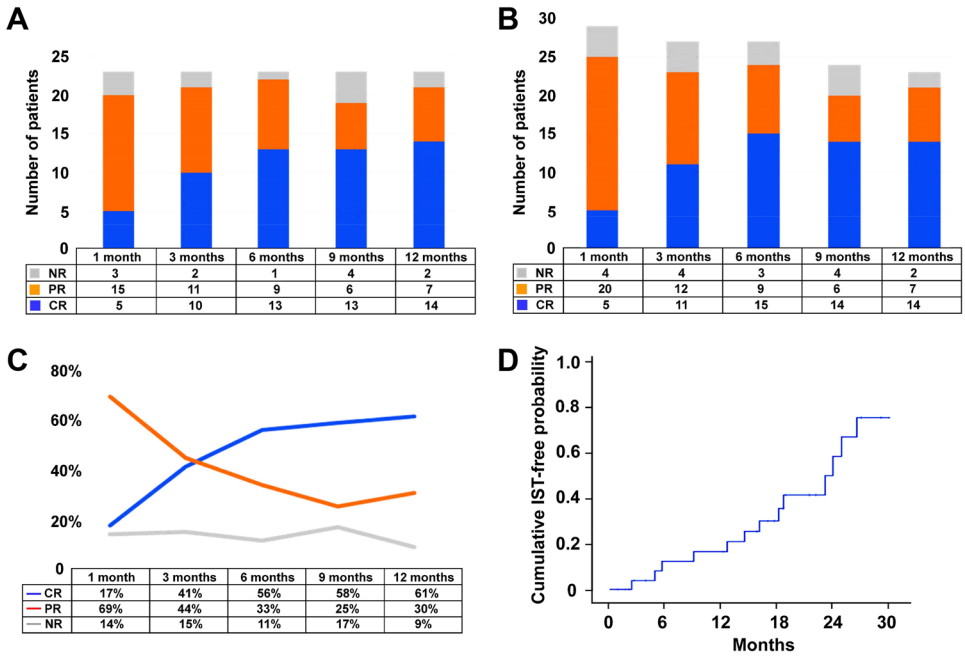

Fig. 3 Outcome of patients with chronic graft-versus-host disease treated with ruxolitinib**. A** Reponses with time in patients with a follow-up duration of more than 12 months ($N=23$). CR: complete response; PR: partial response; NR: no response. **B** Responses with time in the entire cohort of patients ($N=29$). **C** Probabilities of responses in the entire cohort of patients. **D** Probabilities of freedom from immunosuppressive therapy (IST)

Discussion

We showed high response rates of ruxolitinib in the treatment of aGVHD and cGVHD. In previous studies of ruxolitinib in aGVHD, variable responses were observed. In eight reported series comprising 238 patients (supplemental file 6) [7, 13–18], the ORRs varied from 45 to 84%, and CR varied from 9 to 67%. Such disparate results were due to differences in patient selection, timing of treatment, disease definition and more importantly response criteria. In this study, we evaluated our patient according to a standard set of recently proposed definitions and response criteria of aGVHD [20]. Hence, our results will be comparable with other studies in which these standard aGVHD definitions are adopted. We achieved an ORR of 89%, and CR at day 28 of 35% in our patients. Importantly, continued ruxolitinib treatment beyond day 28 upgraded the responses in PR patients, so that CR finally occurred in 69% of cases. Moreover, CR allowed complete tapering of IST in 13/18 patients (72%). However, 28% of CR patients developed

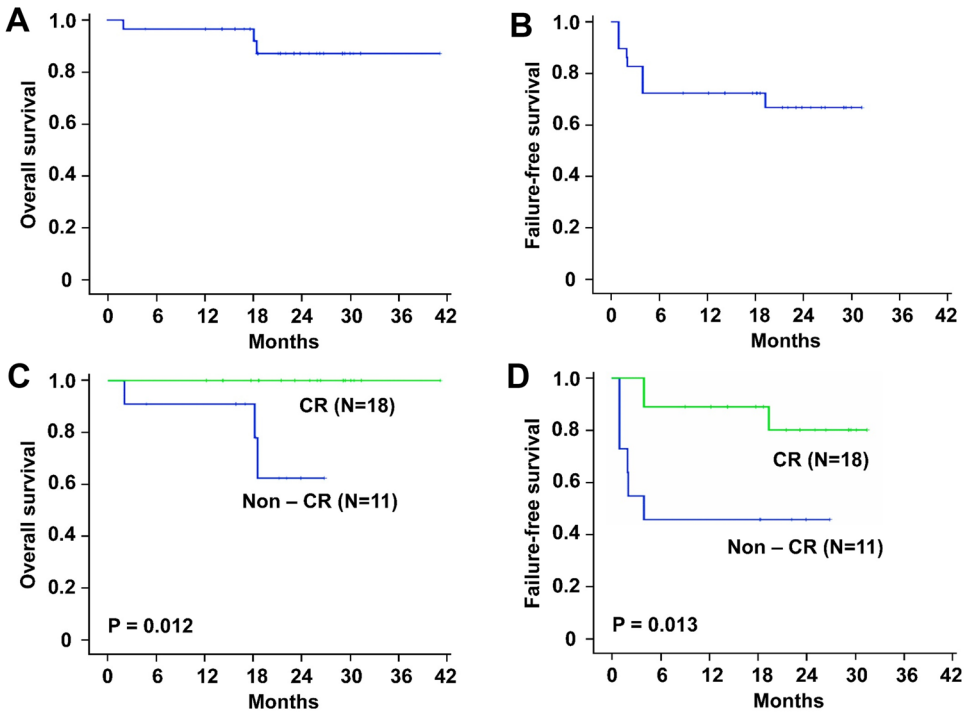

Fig. 4 Survival curves of patients with chronic graft-versus-host disease treated with ruxolitinib. CR: complete response

cGVHD while still receiving ruxolitinib. Multivariate analysis showed that CR was the only factor significantly associated with superior survivals.

For cGVHD, reported results of ruxolitinib treatment were also variable. In eight published series comprising 268 patients (supplemental file 6) [7, 10–12, 14–16, 18], the ORR ranged from 43 to 100%, and CR ranged from 5.5 to 26%. Heterogeneity in study designs accounted for these differences. Furthermore, the time-point of response assessment significantly affected the reported results. In our cohort, although the ORR remained at about 80% from 1 to 6 months, the CR rate increased from 16% at 1 month to 48% at 6 months. Our relatively high CR rates might be related to the inclusion of "mild" cases and proportionally fewer severe cases. In fact, in the REACH3 study, where ruxolitinib was compared with BAT for SR/D-cGVHD, response was also assessed at or after 6 months [6]. The achievement of CR in cGVHD was important for several reasons. Only CR patients maintained their responses with time, whereas there was a continuous loss of response in PR patients. Furthermore, tapering of IST was only possible in CR patients. Finally, similar to aGVHD, CR was the only factor impacting positively on survivals in cGVHD patients.

In both aGVHD and cGVHD, we observed an increase in CR with continued ruxolitinib treatment after the first month. It is therefore important to persist with ruxolitinib therapy to optimize benefit. However, our patients reached their maximal response at 6 months, with no further increase in CR after this time. Furthermore, PR patients might lose their response beyond this point. Therefore, for patients who only achieve PR after six months of ruxolitinib treatment, additional agents ought to be used, in order to maintain response and possibly improve outcome.

In our cohort, certain complex subtypes of GVHD were not present. These included thrombotic microangiopathy complicating aGVHD, and bronchiolitis obliterans syndrome (BOS) and scleroderma in cGVHD. Limited data suggest that ruxolitinib might be useful in BOS [24] and sclerodermatous lesions complicating cGVHD [25]. Prospective studies are needed to define if ruxolitinib treatment might be efficacious in such conditions.

In conclusion, SR/D aGVHD and cGVHD showed good responses to ruxolitinib in routine practice outside a trial setting. Further studies are needed to define if moving ruxolitinib forward in the treatment algorithm may be feasible and beneficial, particularly in preventing progression of aGVHD to cGVHD, and avoiding some of the irreversible sequelae of cGVHD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00277-021-04658-x.

Author contribution Garret M.K. Leung: clinical management, data analysis, manuscript writing and approval.

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Albert K.W. Lie: clinical management, manuscript writing and approval.

Eric Tse: clinical management, manuscript writing and approval.

Yok-Lam Kwong: clinical management, manuscript writing and approval.

Declarations

Ethical approval The study was approved by the Institute Review Board.

Informed consent The patients gave informed consent.

Conflict of interest The authors declare that they have no conflict of interest.

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