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Utilisation du ruxolitinib dans la GVH aigüe cortico-résistante de l'enfant, une étude multicentrique du groupe pédiatrique de la SFGM-TC

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THÈSE D'EXERCICE / UNIVERSITÉ DE RENNES 1
sous le sceau de l'Université Bretagne Loire

Thèse en vue du
DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

présentée par

Louise LAISNÉ

Née le 28-05-1990 à Aix en Provence

**Utilisation du
ruxolitinib dans la
GVH aigüe cortico-
résistante de
l'enfant, une étude
multicentrique du
groupe pédiatrique
de la SFGM-TC**

Thèse soutenue à Rennes

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devant le jury composé de :

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RUXOLITINIB IN CHILDREN WITH STEROID REFRACTORY ACUTE GRAFT VERSUS HOST DISEASE: A MULTICENTER STUDY OF THE PEDIATRIC GROUP OF SFGM-TC

SHORT TITLE: RUXOLITINIB IN PEDIATRIC GRAFT VERSUS HOST DISEASE.

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ABSTRACT

We conducted a national multicenter retrospective study in France to evaluate efficacy and tolerance of ruxolitinib in children with steroid-refractory acute graft-versus-host disease (aGVHD) after allogeneic hematopoietic stem cell transplant. Patients were recruited from the 15 pediatric transplantation centers in France. Transplanted patients were eligible if they met the following criteria: aged ≤ 18 years at transplantation, receiving a myeloablative allogeneic haematopoietic stem cell transplant irrespective of the stem cell source, having an acute GVHD of grade ≥ 2 and treated with ruxolitinib for steroid refractory acute GVHD. Treatment failure was defined by the absence of improvement of aGVHD, deterioration of aGVHD in any organ by at least one stage, the development of acute GVHD manifestations in a previously unaffected organ, and the use of any additional agents to control the disease. Twenty-nine patients received ruxolitinib for steroid-refractory aGVHD. Six patients achieved a complete response at day 28 after the start of treatment but finally 19 patients (65.5%) achieved a CR with a median delay of 41 days (5 to 93 days). Two patients had a partial response. All patients who achieved CR or PR discontinued corticosteroid treatment. Eight patients showed treatment failure. Overall response rate was 72.4%. Twenty three of 29 patients were alive at a median follow-up of 685 days (177 to 1042 days) after the HSCT. Viral replication (including CMV, EBV and ADV) was observed in 51.7% of cases. We did not observe severe hematological adverse events and cytopenia requiring a modification of ruxolitinib doses always resolved. The median initial dose of ruxolitinib was 12.6 mg/m²/day with a huge range (6.3 to 28.7 mg/m²/d). We could not demonstrate any relationship between initial dose and effectiveness. Ruxolitinib may constitute a promising second line treatment for children with steroid-refractory aGVHD that should be validated in prospective large-scale pharmacokinetic and efficacy trial.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) remains the only curative treatment in a number of pediatric hematological pathologies despite acute and long term toxicities. Acute graft-versus-host disease (aGVHD) is an important cause of morbidity and mortality in patients receiving HSCT. Its incidence is estimated about 30%, leading to death in 10 to 20% of aGVHD cases [1,2].

The prognosis of patients with aGVHD depends mainly on the response to steroid treatment, which is known to be effective in approximately 50% of cases [3]. Indeed the mortality rate of steroid refractory or recurrent aGVHD remains as high as 50 to 70% [4].

There is currently no standardized second line strategy for steroid-resistant aGVHD. Several immunosuppressive therapies are used in this indication with variable response rates in childhood. Monoclonal anti-TNF α (infliximab) have been shown to have response rates between 30% and 60%, however relapse at discontinuation was very common (approximately 80%)[5,6]. Alentuzumab shows similar response rates (50 to 70%) but mainly effective in cutaneous GVHD [7]. Response rates are similar for the other molecules commonly used with 53% for basilizumab [8], 46% for daclizumab [9] and 57% for sirolimus [3]. On the other hand, extracorporeal photopheresis has also been used, particularly in cutaneous aGVHD with a response rate of 30 to 85% (depending on the severity of the initial GVHD) but remains difficult to perform in young children [3].

Recently, JAK signaling has been shown to be instrumental in multiple steps leading to inflammation and tissue damage in GVHD [10]. Thus, JAK 1 is involved in the signal transmission of several cytokines, in particular IL-2, IL-6 and INF- γ [11]. First use of ruxolitinib, a selective JAK 1/2 inhibitor, in the treatment of adult steroid-refractory aGVHD, has been reported in 2015 by R Zeizer [12]. A response rate of 81% in aGVHD was achieved in this study leading to promises.

Few data on the efficacy of ruxolitinib in pediatric steroid-refractory aGVHD have also been reported but concerned only a small number of patients from a single center [13].

Prospective trials are underway but results are not known to date [14]. Furthermore, most of these studies planned to include mainly adult patients and only children over 12 years-old. The pediatric use of ruxolitinib in steroid refractory aGVHD remains therefore poorly documented to date.

We conducted a national multicenter retrospective study in France to evaluate efficacy and tolerance of ruxolitinib in children with steroid-refractory aGVHD.

PATIENTS AND METHODS

We retrospectively analyzed all children treated by ruxolitinib for steroid-refractory aGVHD between March 2014 and January 2017. Patients were recruited from the 15 pediatric transplantation centers in France.

Patients

Transplanted patients were eligible if they met the following criteria: aged ≤ 18 years at transplantation, receiving a myeloablative allogeneic haematopoietic stem cell transplant irrespective of the stem cell source, having an aGVHD of grade ≥ 2 , occurred before day 100 after HSCT and treated with ruxolitinib for steroid refractory aGVHD.

This study was approved by the ethics committee of the CHU of Rennes, France

Diagnosis of Steroid-Refractory Acute GVHD and use of ruxolitinib

GVHD was staged according to Glucksberg-scale .

GVHD was defined steroid-refractory when GVHD symptoms were resistant to treatment with methylprednisolone (≥ 1 mg/kg/day) given for at least 7 days .

The majority of patients were treated with ruxolitinib as an add-on immunosuppression therapy. As pediatric dosing of ruxolitinib in aGVHD is unknown (no marketing authorization in this indication), starting dose for the youngest was 5 mg/day but doses were variable according to centers and tolerance. Ruxolitinib was given orally BID. As a general rule according to dosing recommendations, gradual tapering of the dose of ruxolitinib was considered (decrease or spacing daily dosage) [11].

Treatment response

Response was evaluated according to previously defined diagnostic criteria for aGVHD.

Treatment responses were categorized as complete response (CR), partial response (PR) or treatment failure. A CR to ruxolitinib was defined as the absence of any symptoms related to GVHD. A PR was defined as the improvement of at least one stage in the severity of aGVHD in one organ without deterioration in any other organ. A response had to last for at least 3 weeks. Treatment failure was defined by the absence of improvement of aGVHD, deterioration of aGVHD in any organ by at least one stage, the development of aGVHD manifestations in a previously unaffected organ, and the use of any additional agents to control the disease.

Patients were scored at day 28 for their best response and for their best overall response at any time after starting treatment with ruxolitinib, with follow-up censored at the onset of any subsequent systemic immunosuppressive therapy.

Toxicity and tolerance assesement

In this retrospective study, we only focused on hematological and infectious toxicities because they are the most frequently described in previous reports and because other adverse events were very challenging to report in such a retrospective study.

Hematological toxicity was considered as significant when thrombocytopenia an/or neutropenia lead to a dose adjustment of ruxolitinib.

Blood cytomegalovirus, Epstein-Barr virus and adenovirus PCRs were performed twice weekly per routine and any positive value was considered to indicate viremia. Any grade III or IV infectious complication was also collected as a significant infectious complication.

Statistics

Univariate logistic regressions were conducted to model the response (complete versus no complete response either partial response or failure). Factors with a significance of $p < 0.20$ during univariate analyzes were included in a multivariate model, then a step-by-step selection was performed to obtain a final multivariate model. Significance was defined as $p < 0.05$.

RESULTS

Patients

Twenty-nine patients of median age 4.3 years (range 0.6 to 14.5) received ruxolitinib for steroid-refractory aGVHD, of which 16/29 (55.2 %) were under 6 years old (median age: 2.4 years and median weight: 13.2 kg).

Table 1 shows patients and transplants characteristics.

Organs involved

14 out of 29 patients (48.3%) have multiple organ involvement. Organs involved included gastrointestinal tract (GI) (n=7); skin (n=7); liver (n=1); GI and liver (n=3); skin and GI (n=5), and other skin aGVHD combined (n=6). Few patients gathered typical acute GVHD organ involvement and further developed chronic GVHD organ lesions.

GVHD characteristics

Acute GVHD was diagnosed at a median of 21 days (range, 10 to 100) after HSCT and ruxolitinib was started at a median of 91 days (range, 17 to 518) after HSCT.

Table 2 shows GVHD characteristics.

Prior management

The median number of immune suppressive agents received before initiation of ruxolitinib, with exclusion of agents used for acute GVHD prophylaxis was 2 (range, 1 to 6) for the overall cohort. Two periods could be divided. Patients who received a HSCT from 2014 to 2015 (n=18) started ruxolitinib in third line (range, 1 to 6) and those who received a HSCT from 2016 to 2017 (n=9) in second line (range, 1 to 4). The various treatment used were reported in table 2. Only three patients (all with skin aGVHD) started ruxolitinib in second line at a median of 37 days (28-55) after transplant.

Details of ruxolitinib (mg/m²/day) administration according to body weight, age, involved organs are listed in supplemental table 1.

Response

We evaluated 29 patients for response to ruxolitinib.

Complete response

Only 6 patients achieved a CR at day 28 after the start of treatment with ruxolitinib but finally 19 patients (65.5%) achieved a CR with a median delay of 41 days (5 to 93).

Out of the 19 patients who achieved CR, 17 discontinued ruxolitinib after a median time of 216 days (range, 70 to 575) and 2 are still treated at the date of the latest news. The median follow-up time for these 17 patients was 685 days (range, 177 to 1042). Best response was lasting after stopping ruxolitinib because only 1/17 relapsed.

Interestingly, the response rate in the population less than 6 years old (16/29) tended to be higher with 81.3% overall response (75% CR and 6.3% PR) ($p = 0.2453$). Complete response was also obtained for the three patients who benefited from ruxolitinib in second line treatment, in a delay of 18 days (5-42).

Partial response

Two patients showed a partial response to ruxolitinib, with the best response observed for one after 34 days and the other after 101 days. One of these patients died under ruxolitinib and the other one is always treated on the last follow-up date (04-18).

Management of corticosteroids after introduction of ruxolitinib

All patients who achieved CR (except 2 missing data) discontinued corticosteroid treatment after a median time since the introduction of ruxolitinib of 82 days (22 to 464 days).

Among the 2 patients who achieved PR, 1 discontinued corticosteroid treatment prior to the introduction of ruxolitinib, the other one after 15 days.

Treatment failure

Eight patients were deemed to be treatment failures. Ruxolitinib was stopped in each. The median duration of treatment with ruxolitinib was recorded for 4/8 and ranged from 43 to 236 days with a median duration of 183 days.

The causes of treatment failure are progression of GVHD under ruxolitinib requiring introduction of an additional immunosuppressive treatment for 7 patients and death under ruxolitinib for 1 patient (multi-visceral failure and graft rejection).

Overall survival

Twenty three of 29 patients were alive at a median follow-up of 685 days (177 to 1042 days) after the HSCT and 480 days (93 to 829 days) after the start of treatment with ruxolitinib. Causes of death in 6 children included 1 relapses of the initial pathology, 2 infections (1 adenovirus infection, 1 refractory sepsis with pseudomonas aeruginosa), 2 worsening of GVH and 1 graft rejection.

We could not find any association of baseline characteristics and CR/PR to ruxolitinib (Table 3).

Ruxolitinib dosing

All patients started treatment in 2 doses per day.

The median initial dose of ruxolitinib was 12,6 mg/m²/day with a huge range (6.3 mg/m²/d to 28.7 mg/m²/d) especially for the 16 children (55.2%) under 6 years old (Figure 1). The median initial dose was comparable for children over or under 6 years old, respectively 12,6 and 12,8 mg/m²/day.

We could not demonstrate any relationship between initial dose and effectiveness (Figure 2). The delay to reach the best response was not either influenced by dosage.(Figure 3)

Adverse effects

Viral replication

Fifteen patients (51.7%) did not present any viremia. Viral replication has been reported in 12 patients (41.4 %) including cytomegalovirus (n=5, 17.2 %), Epstein-Barr virus (n=3, 10.3 %), adenovirus (n=2, 6.9 %) and combined replication (n=2, 6.9 %). Data were not available for 2 patients. Except for one patient who died of adenovirus infection, appropriate antimicrobial agents could treat all patients successfully, without stopping ruxolitinib.

Hematological toxicities

We did not find any neutropenia or anemia requiring adjustment of the dose of ruxolitinib. Three patients (10.3%) having pronounced thrombocytopenia required dose reduction of ruxolitinib. Two of these presented a CR despite dose reduction.

DISCUSSION

The management of steroid refractory or recurrent aGVHD after HSCT is challenging and there is no standardized second line strategy.

We conducted a retrospective national study to evaluate efficacy and safety of ruxolitinib in children with steroid refractory aGVHD. We showed that the overall response rate was 72.4% (21/29) with complete response in 65.5% of cases. The response rate even reached 81.3% for the 16 children less than 6 years old. Our results in a series of severe GVHD (75.9 % grade 3 and 4) are comparable with those published by Zeiser *et al* in adulthood [12], and promising. Indeed, other second line agents used for steroid refractory aGVHD in children such as infliximab, basiliximab, daclizumab or alemtuzumab, inconstantly reach 50% of complete response [5-7-8-9]. Nevertheless our response rate at the time point "day 28" is poorer than in the childhood study of Khandelwal *et al* [13]. As in a second or more line setting, therapy that benefits most patients is the crucial point, we have chosen not to consider this time point as the principal endpoint but the response rate at any time. Thus, we showed that response could be obtained in less than one week and frequently in about 1.5 months. In all children with CR or PR, corticosteroids could have been stopped and common adverse effects related to prolonged use have been saved.

We could not find any predictive factor for the efficacy of ruxolitinib with respect to the patient, the graft modalities or the GVHD characteristics. Our study also demonstrated that ruxolitinib was effective in gut

aGVHD with a response rate as high as 65% which was an issue because oral administration of ruxolitinib.

These encouraging results have led during the time period of the study to an earlier use of ruxolitinib (third to second line after steroid failure) in the treatment strategy of steroid refractory aGVHD. We may assume that for the 2 patients who died of aGVHD in our study, the introduction of ruxolitinib was too late to be effective because the time between the HSCT and the introduction of ruxolitinib was longer than the median (from 265 days and 181 days for a median to 110 days). The appropriate time of introduction of ruxolitinib remains to be defined.

Appropriate dosage of ruxolitinib remains also unknown because we could not demonstrate any significant relationship between dosage of ruxolitinib and either rate of efficacy or speed of efficacy on GVHD. Individual blood samples using appropriate model based approaches should be implemented for right dosage adjustment because ruxolitinib interferes with CYP450 (the administration of inhibitors of CYP450 was not recorded in our study). The lack of this pharmacokinetic approach is a limitation of our study. The pharmacokinetic data might be given by REACH studies which are underway to compare ruxolitinib with best available therapy in the treatment of corticosteroid resistant aGVHD (15). Nevertheless, these studies did not still include patients younger than 12 years-old whereas our large pediatric study reported new data about young children.

In the other hand, the safety profile of ruxolitinib was rather favorable. We did not observe severe hematological adverse events and cytopenia requiring a modification of ruxolitinib doses always resolved. Viral replication (including CMV, EBV and ADV) was observed in 54% of cases indicating that viral replications need to be closely monitored. This rate should be interpreted with caution because a comparable frequency of viral replications was reported in children treated with other immunosuppressive drugs including infliximab, alemtuzumab and daclizumab [5-7-9].

In conclusion, ruxolitinib demonstrates high CR rates especially in children less than 6 years old and may be considered as a possible second-line agent for the treatment of corticosteroid resistant aGVHD, including cases of gastrointestinal involvement or severe GVHD. A future prospective large-scale pharmacokinetic and efficacy studies are needed to define the appropriate role of JAK 1/2 inhibition in steroid refractory aGVHD in pediatric HSCT recipients.

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FIGURE LEGENDS

Figure 1. Initial dosage of ruxolitinib. The median initial dose of ruxolitinib was 12.6 mg/m²/day given orally BID with a huge range (6.3 mg/m²/d to 28.7 mg/m²/d) especially for the 16 children (55.2%) under 6 years old

Figure 2. Dosage of ruxolitinib according to the response. There is no relationship between initial dosage of ruxolitinib and effectiveness

Figure 3. Response time according to the initial dosage of ruxolitinib (inferior or superior at the median initial dose, 12.6 mg/m²/day). The time to reach the best response is not influenced by the initial dose of ruxolitinib

Table 1. Patient demographics

Variables	absolute number (%)
Gender	
Female	8 (27.6)
Male	21 (72.4)
Disease	
Acute leukemias	10 (27.6)
Other hematological malignancies	3 (10.3)
Myelosuppression	2 (6.9)
Immune deficits *	10 (27.6)
Metabolic diseases **	2 (6.9)
Others ***	2 (6.9)
CMV Status	
R-/D-	9 (31.0)
R-/D+	5 (17.2)
R+/D-	5 (17.2)
R+/D+	10 (27.6)
Source of stem cells	
Bone marrow	20 (69.0)
cord blood unit	7 (24.1)
peripheral stem cells	1 (3.4)
Bone marrow + cord blood unit****	1 (3.4)
Conditioning	
TBI+	6 (20.7)
TBI-	23 (79.3)

TBI : total body irradiation

R: recipient

D: donor

*1 chronic congenital neutropenia , 1 Purtilo syndrome, 2 IPEX syndrome , 1 Wiskott-Aldrich syndrome, 5 severe immunodeficiency

** 1 krabbe disease, 1Hurler disease

*** 1 Thalassemia, 1 X-linked alveolar proteinosis

**** Cord blood unit from the pregnancy of her sister, bone marrow donor

Table 2. GVHD characteristics

Variables	Absolute number (%)
Maximum grade of GVH	
1	0 (0)
2	7 (24.1)
3	13 (44.8)
4	9 (31.0)
Grade of GVH at J1 of ruxolitinib	
1	0 (0)
2	11 (37.9)
3	13 (44.8)
4	3 (10.3)
Not available	2 (6.9)
GVH prophylaxis	
Cyclosporine	4 (13.8)
Cyclosporine + Cellcept	13 (44.8)
Cyclosporine + methotrexate	4 (13.8)
Other*	8 (27.6)
Curative treatment of GVH	
Corticoids**	29 (100)
Infliximab	13 (48.1)
Mycophenolate mofetil	11 (40.7)
Extracorporeal photopheresis	5 (18.5)
Other***	21 (77.8)

GVHD : Graft versus host disease

* mycophenolate mofetil and methylprednisolone (n=2) ; cyclosporine, methylprednisolone and anti lymphocyte serum (ALS)(n=1) ; cyclosporine and ALS (n=1) ; T depletion (n=1); cyclosporine, mycophenolate mofetil and methylprednisolone (n=1) ; cyclosporine mycophenolate mofetil, methotrexate and rapamycin (n=1) ; cyclosporine and rituximab (n=1)

** 2 mg/kg/day except for 2 (1 mg/kg/day)

*** inolimomab (n=4), sirolimus (n=4), antithymoglobulines (n=3), tacrolimus (n=3), methotrexate (n=2), cyclosporine (n=2), bolus of corticosteroids (n=2), basiliximab (n=1)

Table 3. Univariate analysis for association of baseline characteristics and CR/PR to ruxolitinib

	CR/PR	Failure	OR [IC95%]	P
Number of patients	21	8		
Age				p = 0.2453
< 6 years	13	3	1	
> 6 years	8	5	0.37 [0.07-1.98]	
Weight				p = 0.9759
<15 kg	7	3	1	
15-30 kg	11	4	1.18 [0.20 ; 6.93]	
>30 kg	3	1	1.29 [0.09 ; 17.95]	
Isolated skin aGVHD				p = 0.5091
No	16	7	1	
Yes	5	1	2.19 [0.21 ; 22.34]	
GI aGVHD				p = 0.6433
No	6	3	1	
Yes	15	5	1.50 [0.27 ; 8.34]	
Source of stem cells				p = 0.9733
Bone marrow	13	7	1	
2 cord blood units	1	0	1.71 [0.02 ; 177.36]	
Peripheral stem cells	1	0	1.71 [0.02 ; 177.36]	
Bone marrow + cord blood unit	1	0	1.71 [0.02 ; 177.36]	
Cord blood unit	5	1	2.04 [0.24 ; 17.56]	
Gender				p = 0.1402
Female	8	0	1	
Male	13	8	0.09 [0.00 ; 2.18]	
Regimen with TBI				p = 0.7243
No	17	6	1	
Yes	4	2	0.71 [0.10 ; 4.89]	
Number of immune suppressive agents before use of ruxolitinib				p = 0.5377
2 or less	11	3	1	
3 or more	10	3	1.82 [0.27 ; 12.17]	
Grade max of aGVHD				p = 0.4056
2	5	2	1	
3	11	2	2.09 [0.25 ; 17.73]	
4	5	4	0.56 [0.07 ; 4.40]	

CR : complete response

PR :partial response

aGVHD: acute graft versus host disease

TBI: total body irradiation

Figure 1.

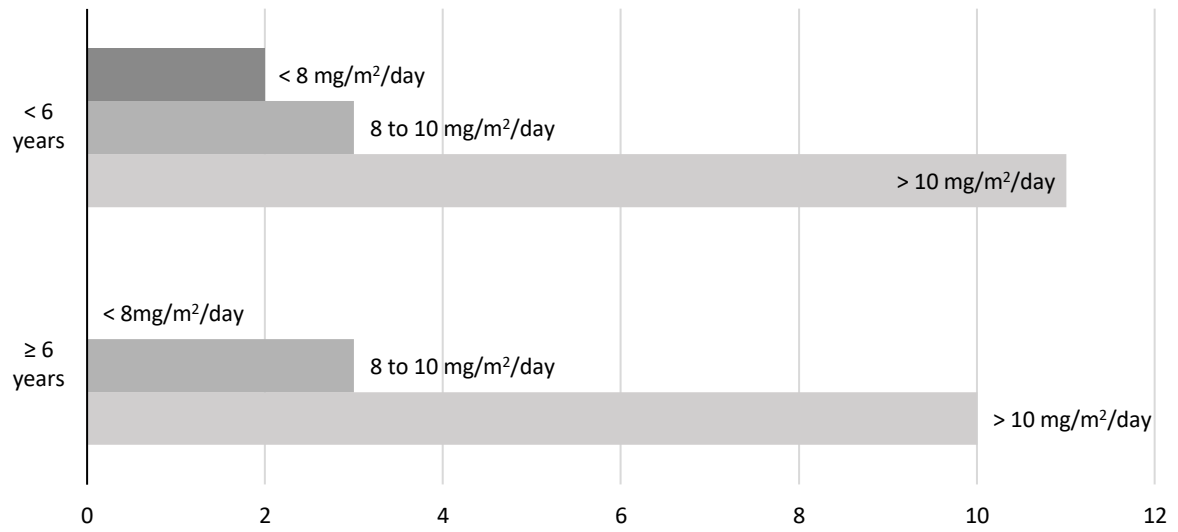


Figure 2.

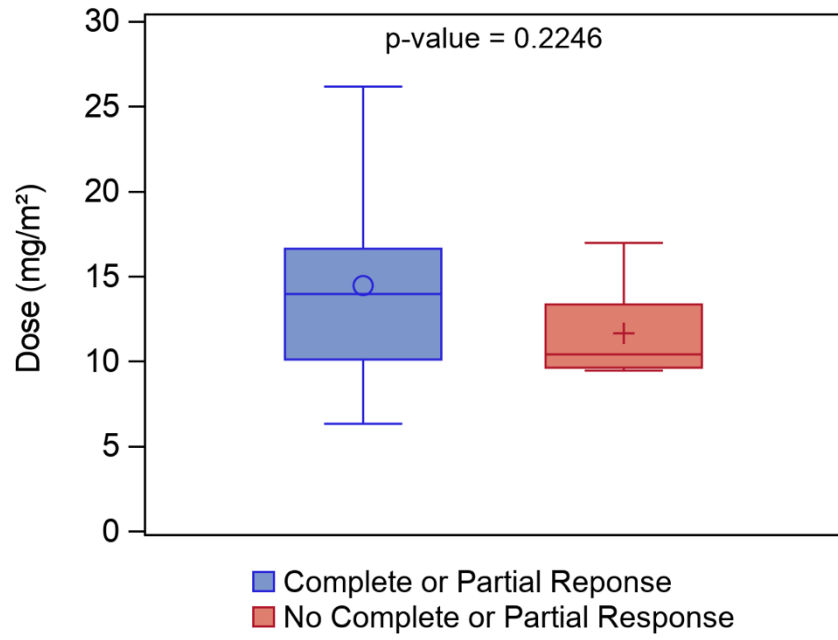
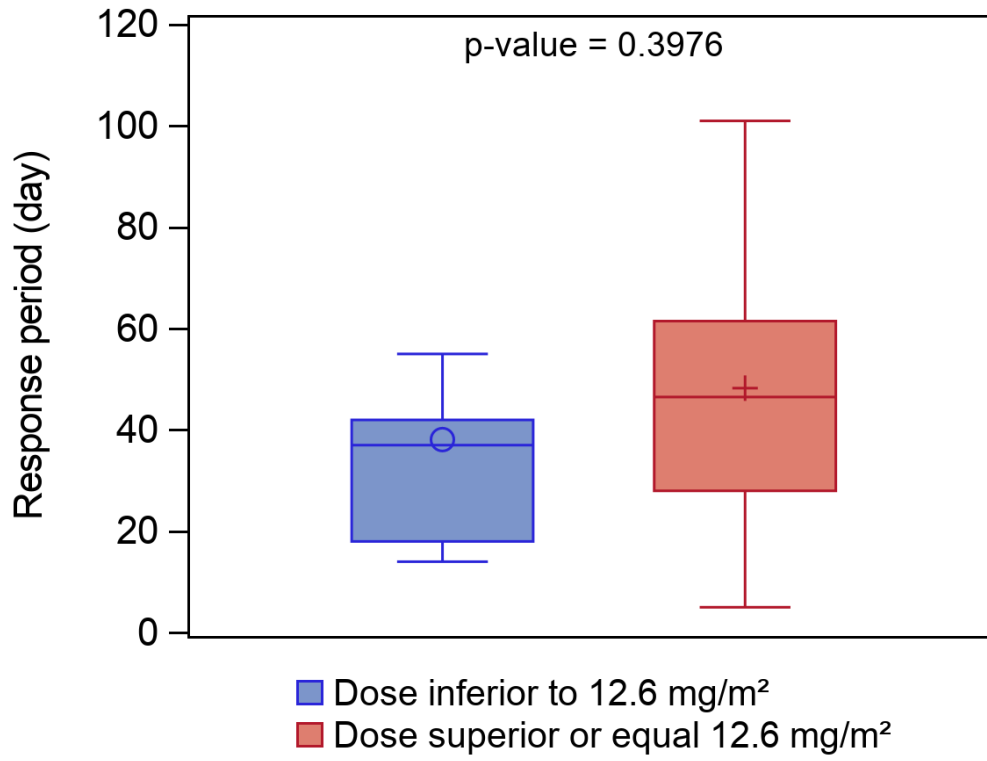


Figure 3.



Supplemental Table 1. Details of ruxolitinib (mg/m²/day) administration according to body weight, age, involved organs

Patient	Age at D1 of HSCT (years)	Weight at D1 of HSCT (kg)	Organs involved	Dosage of ruxo at D1 (mg/day)	Dosage of ruxo at D1 (mg/m ² /day)
1	5.1	16.9	Skin, GI	20	28.7
2	7.6	22.0	GI	20	23.6
3	2.5	13.5	Skin, GI	10	17.0
4	11.0	36.2	GI	20	16.6
5	6.8	19.1	Skin	20	26.2
6	8.4	20.0	Skin, GI, BM, Eyes	10	12.6
7	1.3	9.5	Skin	10	22.1
8	14.5	73.5	GI	20	10.9
9	2.8	13.7	Skin, GI	10	16.8
10	14.3	37.8	Skin, GI, liver	10	8.1
11	1.7	12.9	GI	5	8.8
12	14.4	47.0	Liver	20	14.1
13	11.8	27.0	Liver, GI	10	10.2
14	6.7	20.0	Skin, GI, lung, joints	10	12.6
15	3.8	15.0	GI	5	7.8
16	1.2	11.2	Skin	5	9.8
17	1.3	10.0	Skin, GI, liver	5	10.6
18	3.8	16.4	Skin, GI	10	14.7
19	3.8	20.0	Skin, kidneys	5	6.3
20	7.3	29.3	Liver, GI	10	9.6
21	7.8	23.2	Skin	10	11.3
22	4.3	17.5	Liver, GI	10	14.0
23	0.6	6.8	Skin, GI	5	14.2
24	0.6	6.9	Skin	5	14.0
25	2.4	11.7	Skin	5	9.5
26	12.6	29.1	Skin, lung	10	9.7
27	3.7	22.2	Skin	10	11.7
28	6.4	15.2	GI	10	15.5
29	1.1	10.7	GI	5	10.1

LAISNE Louise – Utilisation du ruxolitinib dans la GVH aigue cortico-résistante, une étude multicentrique du groupe pédiatrique de la SFGM-TC

34 feuilles. 4 tableaux, 3 figures, Thèse : Médecine ; Rennes 1; 2019 ; N° .

Résumé français

Nous avons mené une étude rétrospective multicentrique nationale française pour évaluer l'efficacité et la tolérance du ruxolitinib chez les enfants atteints de maladie du greffon contre l'hôte (GVH) aiguë cortico résistante après greffe allogénique de cellules souches hématopoïétiques. Vingt-neuf patients ont été inclus. Dix-neuf patients (65,5%) ont obtenu une réponse complète avec un délai médian de 41 jours (5 à 93). Deux patients ont eu une réponse partielle et 8 patients étaient en échec thérapeutique. Le taux de réponse global était de 72,4%. Vingt-trois des 29 patients étaient en vie après un suivi médian de 685 jours (177 à 1042 jours) après la greffe. Une réplication virale a été observée dans 51,7% des cas. Nous n'avons pas observé d'effets indésirables hématologiques graves. Le ruxolitinib pourrait constituer un traitement de deuxième intention prometteur pour les enfants atteints de GVH cortico résistante.

Rubrique de classement : Étude Clinique Rétrospective

Mots-clés : GVH aigue cortico résistante,
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