RESEARCH LETTER

Ruxolitinib is highly effective in steroid-resistant graft-versus-host disease: real-world data from a single center

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Introduction Chronic graft-versus-host disease (cGVHD) remains one of the main causes of late mortality after allogenic hematopoietic stem cell transplantation (allo-HSCT).[1] Symptoms usually develop within months of the transplantation and the disease may affect every organ, leading to its dysfunction. Disease manifestations are heterogenous, and multiple organ involvement is common.

According to the current European Bone Marrow Transplant guidelines, corticosteroids are the only standard first-choice therapeutic approach for newly-diagnosed patients with cGVHD.[2] There is no consensus with respect to the second-line treatment in the case of steroid refractoriness; therefore, selection of subsequent lines differs between centers. Since 2017, only 3 drugs have received the Food and Drug Administration approval in this indication: ibrutinib, ruxolitinib (RUX), and belumosudil.[3] Other commonly used agents include calcineurin inhibitors, mycophenolate mofetil, extracorporeal photopheresis (ECP), or rituximab; however, the treatment outcomes are not always satisfactory.

Here, we report real-life data of 21 patients treated with RUX as a salvage therapy for steroid-resistant cGVHD (SR-cGVHD) between the years 2020 and 2022.

Patients and methods **Study population** This retrospective analysis included 21 adult patients who had undergone allo-HSCT in our center and were subsequently treated with RUX as a salvage treatment for moderate-to-severe cGVHD. The patients were treated for cGVHD according to the institutional guidelines. The first-line treatment consisted of oral methylprednisolone (MP). After the diagnosis of steroid refractoriness, doses of MP were gradually reduced. As a second-line treatment, the patients received tacrolimus or mycophenolate mofetil (MMF; in the case of contradictions to the use of calcineurin inhibitors). The following agents were used as subsequent treatments: methotrexate, imatinib, and ECP. Two patients diagnosed with bronchiolitis obliterans received FAM (fluticasone, azithromycin, and montelukast). The study was carried out in accordance with the principles of the Declaration of Helsinki. All patients gave their written informed consent to participate.

Diagnosis of steroid-resistant chronic graft-versus--host disease The 2014 National Institutes of Health (NIH) Grading System was applied for the diagnosis of cGVHD.[4,5] GVHD severity was assessed at the start of the RUX treatment. Steroid refractoriness was defined as: 1) progression of cGVHD while on MP at a dose of 1 mg/kg/day or higher for 1 to 2 weeks; 2) stable cGVHD while on MP at a dose of 0.5 mg/kg/day or higher for at least 4 weeks.[6]

Ruxolitinib dosing and definitions of response RUX was initiated orally at 5 mg twice daily, and the dose was subsequently increased to 10 mg twice daily in 6 patients. Doses of other immunosuppressants were gradually diminished while the patients received RUX. Assessment of response to the RUX therapy was performed following the NIH criteria.[4] Complete remission (CR) was defined as total resolution of cGVHD manifestations; partial remission (PR) was considered as improvement in the score as compared with the baseline, reflecting a real clinical benefit. Other responses, that is, stable disease, progression, or mixed responses were considered as treatment failure.

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Statistical analysis The Kaplan–Meier method was used for plotting the survival curves. Differences between the survival curves were assessed by the log-rank test (or the Mantel–Haenszel test), using the G-rho family of tests. The independence of 2 nominal variables was tested using the Fisher exact test. Simultaneously, effect sizes were estimated by the Yule phi (in the case of 2 dichotomous variables), with the interpretation based on the convention proposed by Funder et al.[7] Categorical data were described by frequencies and percentages, whereas continuous variables were expressed as median and interquartile range. Analyses were conducted using the R Statistical language (version 4.1.1; The R Foundation for Statistical Computing, Vienna, Austria). The significance level of the statistical tests was set at a *P* value of 0.05 or lower.

Results

Patient characteristics A total of 21 patients (14 men and 7 women) with moderate-to-severe SR-cGVHD received the RUX treatment in our center between the years 2020 and 2022. Median age at transplantation was 44 years (range, 21–71 years). The study patients received allografts for acute myeloid leukemia (n = 10), chronic myeloid leukemia (n = 3), chronic myelomonocytic leukemia (n = 2), primary myelofibrosis (n = 2), acute lymphoblastic leukemia (n = 2), severe aplastic anemia (n = 1), or chronic lymphocytic leukemia (n = 1). Eleven patients (52.4%) were transplanted during CR, 1 (4.8%) during PR, and 9 (42.9%) in an active disease stage. Seventeen patients (81%) received allografts from a fully matched donor (either related or unrelated), 3 patients (14.3%) were transplanted from a 9/10 HLA unrelated donor, and 1 individual received a haploidentical transplant. In total, 14 patients (66.7%) received myeloablative conditioning, whereas reduced-intensity conditioning was provided for 7 individuals (33.3%). Antithymocyte globulin was administered in 16 patients before the transplantation. Peripheral blood was the source of stem cells in all patients. GVHD prophylaxis consisted of a calcineurin inhibitor alone (n = 12), a calcineurin inhibitor and MMF (n = 7), MMF alone (n = 1), or post-transplant cyclophosphamide (n = 1). A total of 16 patients (76.2%) had a previous history of acute GVHD (aGVHD), of whom 4 (19%) developed advanced grade III–IV disease.

Baseline characteristics of chronic graft-versus--host disease The median time from allo-HSCT to the onset of cGVHD was 238 days (range, 107–4018 days). Eleven patients (52.4%) had moderate and 10 (47.6%) had severe cGVHD at the time of RUX initiation. All patients were steroid-refractory. The median number of involved organs was 3 (range, 1–4). Skin was the most commonly affected organ (n = 16 [76.2%]), followed by oral mucosa (n = 10 [47.6%]) and eyes (n = 9 [42.9%]). The liver, musculoskeletal system, gastrointestinal tract, and lungs were affected in 28.6%, 14.3%, 14.3%, and 9.5% of the patients, respectively. The median number of previous immunosuppressive lines of treatment was 2 (range, 1–4).

Ruxolitinib efficacy and survival outcomes RUX was started at a median of 370 days after allo-HSCT (range, 61–5153 days). Two patients received RUX for SR-aGVHD and continued the therapy for cGVHD. The median duration of the RUX treatment was 149 days (range, 28–644 days). The overall response rate (ORR) was 76.2% (16 out of 21 patients), including 2 patients with CR and 14 patients with PR.

The 1-year overall survival (OS) among the patients with SR-cGVHD treated with RUX was 82.1% (95% CI, 65%–100%), as presented in FIGURE 1A. There was no significant difference in the 12-month OS between the RUX responders (83.1%; 95% CI, 64%–100%) and nonresponders (80%; 95% CI, 52%–100%) (FIGURE 1B). The patients with severe cGVHD had significantly lower OS than those with moderate disease (64.8%; 95% CI, 39%–100% vs 100%; 95% CI, 100%–100%; $P = 0.045$) (FIGURE 1C).

Overall, 90.9% of the patients with moderate cGVHD (10 out of 11) positively responded to the RUX therapy, whereas in the group with severe cGVHD the response rate was in 60% (6 out of 10). Partial or complete remission of cGVHD symptoms was observed in 80% of the patients with the involvement of 1 or 2 organs (8 out of 10) and in 72.7% of those with involvement of at least 3 organs (8 out of 11). Favorable response to the RUX treatment was seen in 80% of the patients with no history of aGVHD (4 out of 5) and in 75% of those previously treated for aGVHD (12 out of 16). Differences in the response rates across the mentioned subgroups were not significant (FIGURE 1D). The effect size of the treatment response was assessed as large for cGVHD severity and small or very small for the number of involved organs and a history of aGVHD.

The median duration of the follow-up from the onset of cGVHD symptoms was 392 days (range, 57–1373 days). Before the last visit, 4 patients (19%) died. The causes of death included infectious complications (septic shock and pneumonia; n = 2), progression of cGVHD with lung involvement (bronchiolitis obliterans syndrome; n = 1), and relapse of the disease (n = 1).

Infectious complications and hematological toxicities during the RUX treatment were not common—cytomegalovirus reactivation occurred in 3 patients, polyoma BK virus reactivation occurred in 1 individual, 2 patients developed grade 3 thrombocytopenia, and 1 developed grade 3 leukopenia. Relapses were observed in 2 patients.

Discussion

In the absence of standardized treatment guidelines for cGVHD, new approaches remain an unmet need. So far, none of the many available salvage therapeutic options showed any

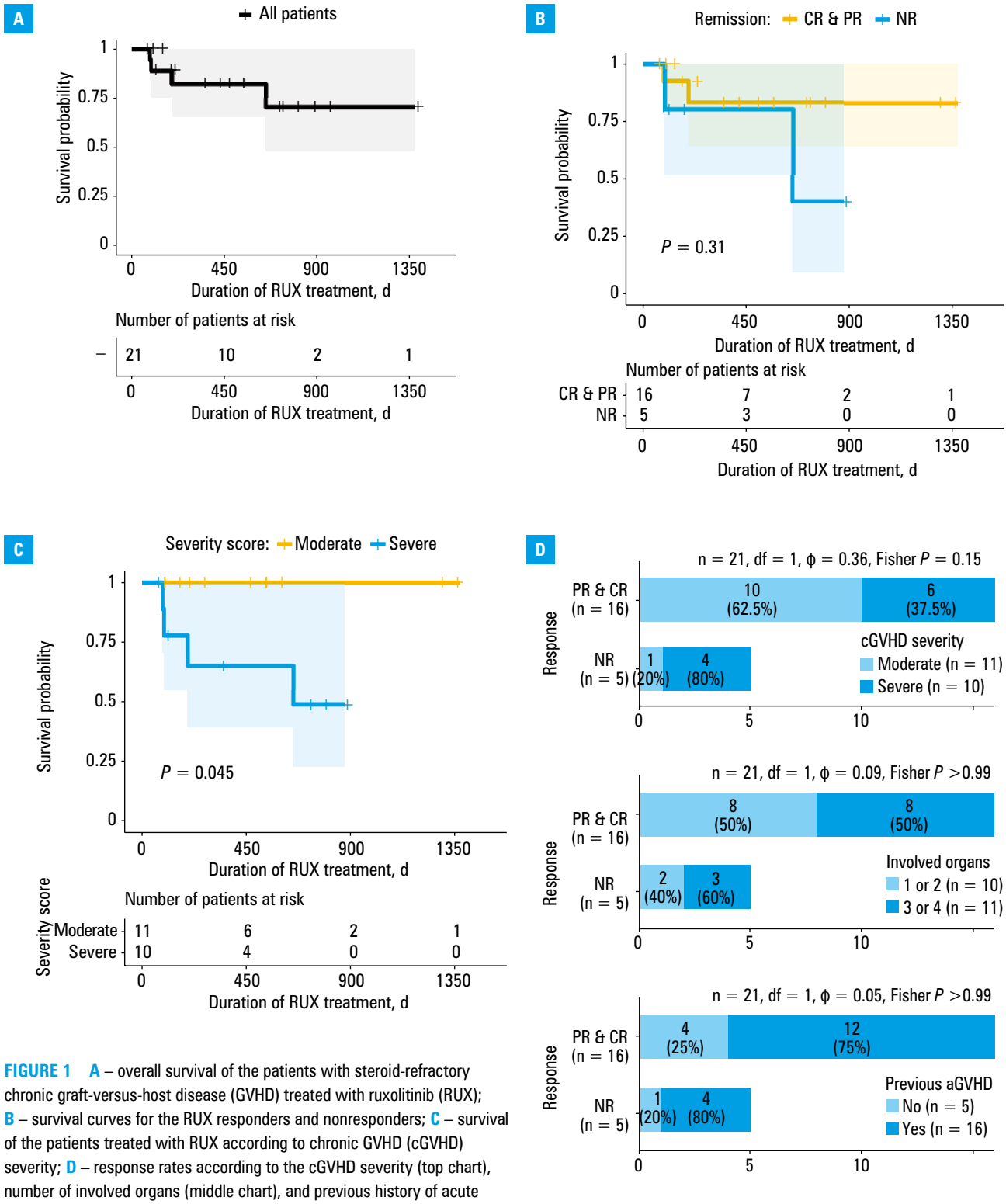

FIGURE 1 **A** – overall survival of the patients with steroid-refractory chronic graft-versus-host disease (GVHD) treated with ruxolitinib (RUX); **B** – survival curves for the RUX responders and nonresponders; **C** – survival of the patients treated with RUX according to chronic GVHD (cGVHD) severity; **D** – response rates according to the cGVHD severity (top chart), number of involved organs (middle chart), and previous history of acute GVHD (aGVHD) (bottom chart)
Abbreviations: CR, complete response; NR, nonresponse; PR, partial response

advantage over the others. RUX, a Janus kinase (JAK) inhibitor, is one of the most promising agents in this setting. In general, its mechanism of action is based on the suppression of proinflammatory signaling and promotion of tolerogenic regulatory T cells.[8]

In 2021, results of the REACH3 clinical trial[9] showed that RUX was an efficient second-line therapeutic choice for steroid-refractory and steroid-dependent patients with moderate or severe cGVHD. This large study including 329 patients proved that treatment with RUX led to a significant improvement in ORR (49.7% vs 25.6%) and symptom relief (24.2% vs 11%) in comparison with 10 other commonly used immunosuppressive drugs. According to other reports, RUX is not only effective as a salvage therapeutic option[10-12] but can also be successfully used as a steroid-sparing agent.[13] Moreover, it is speculated that its efficacy may be even higher when

combined with ECP due to the increasing number of regulatory T cells.[14,15]

In our study, we observed high ORR rates of 76.2%, but most patients met the PR criteria. The most important factor negatively influencing the OS was the severe form of cGVHD. The number of involved organs or previous history of aGVHD had no impact on the response rates. Although there was no significant difference in the 12-month OS between the RUX responders and nonresponders (83.1% vs 80%), further studies with a longer follow-up are needed. Even though RUX is known for its hematologic toxicity through the blockade of JAK2 signaling processes involving thrombo- and erythropoiesis,[8] the safety profile of the drug in our study was satisfactory.

The main limitation of our study was the small sample size. However, it should be mentioned that RUX is not widely available in Poland because it is still not reimbursed. Moreover, RUX is used in a relatively small number of patients, usually when prior therapies fail.

In conclusion, in the real-life setting, RUX was shown to be an effective and well-tolerated treatment option for SR-cGVHD. Its efficacy was demonstrated in a group of heavily pretreated patients in whom other therapeutic options had failed.

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