Updated Findings of a Phase II Study of Ruxolitinib Pre-, during- and Post-Hematopoietic Stem Cell Transplantation for Patients with Primary or Secondary Myelofibrosis

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Background

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  Despite tremendous progress in the treatment of myelofibrosis in the last decade, the only curative therapy remains allogeneic hematopoietic cell transplantation (HCT).
  There are now three FDA-approved JAK inhibitors (JAKi) to treat symptomatic splenomegaly and constitutional symptoms in myelofibrosis, although these agents do not prevent disease progression.
- Discontinuation of JAKi before (pre) HCT is challenging as patients can experience return of symptoms.
- Thus, ruxolitinib is often continued during HCT in an off-label fashion; however, little is known about the safety and efficacy of this approach. Furthermore, there is increasing use of ruxolitinib after (post) HCT, following its approval in treating refractory graft-versus-host disease (GVHD).

Methods

- We previously reported the interim results of a phase II, multicenter, investigator-initiated trial investigating ruxolitinib given pre-, during- and for 1-year post-HCT for patients with primary or secondary MF (NCT03427866).
- Here we present the results of the study with full accrual of 43 patients. The primary endpoint was 1-year GVHD-free, relapse-free survival (GRFS). Secondary endpoints included overall (OS) and progression free survival (PFS), engraftment, and incidence of acute and chronic GVHD.
- Patients were treated with reduced intensity conditioning with fludarabine (30mg/m2/d x 5 days) and melphalan (100 or 140mg/m2 x 1). Patients received peripheral blood stem cell grafts from either 7/8 or 8/8 HLA-matched donors. GVHD prophylaxis consisted of standard tacrolimus and methotrexate.

Results

- 44 patients with myelofibrosis were enrolled and 43 underwent HCT between 9/2018 and 5/2023. Median age was 66 (range 46-75), 37% were female (n=16), and most patients had DIPSS intermediate-2/high risk (n=36), 60% (n=27) were receiving ruxolitinib prior to enrolling on the study. Most (n=35) received 8/8 matched unrelated transplants and had measurable splenomegaly by either ultrasound or CT (n=40) prior to HCT.
- At baseline, 25 patients had JAK2 mutation, 8 had CALR and 5 had MPL mutations, 13 patients had ASXL1 mutations (Figure 1). No differences in outcomes were observed by pre-HCT mutational status. At day 100, all but one patient had undetectable mutations by next generation sequencing.
- The most common grade 3/4 hematologic adverse events (AE) were anemia (n=12),
  thrombocytopenia (14), neutropenia (n=11). Non-hematologic grade 3/4 events included hypertriglyceridemia (n=3).
- Median time to neutrophil engraftment was 15 days (range 4-38), one patient did not engraft. Median time to platelet (>20x109) engraftment was 25 days (range 11-145). At day 30, 2 patients had a donor-cell chimerism below 90% (one ultimately relapsed) and at day 100, 2 patients had chimerism below 90 (one ultimately relapsed). With a median follow up among survivors of 13 months (range 0.7 – 26), 1-year GRFS was 74%. OS, PFS and cumulative incidence of NRM and disease relapse were, 86%, 79%, 10%, and 10%, respectively (Figure 2).
- The cumulative incidence of grade III-IV acute GVHD at 6 months was 2.4%. Only one patient had grade IV acute GVHD. One year moderate/severe chronic GVHD was 11%In univariable analysis, thrombocytopenia of <40 x 109/L pre-HCT was associated with worse OS (1-yr OS: 64% vs 92%, p=0.008). Splenomegaly (defined as >17 cm) was associated with worse PFS (1-yr PFS: 100% vs 64%, p=0.046). There was an improvement in OS in patients that received ruxolitinib and achieved response pre-HCT compared to those that did not but this did not achieve statistical significance (1-yr OS 100% vs 74%, p=0.054).

Conclusions

- This study is the first, multicenter trial to test ruxolitinib use pre-, during- and post-HCT in patients with myelofibrosis. Our results demonstrate safety and feasibility of this approach. Favorable rates of engraftment were observed with ongoing ruxolitinib administration even through hematopoietic nadir.
- We continue to demonstrate favorable outcomes of PFS, OS and GRFS with a low incidence of severe acute and chronic GVHD. Our results strongly support the use of ruxolitinib in the peri- and post-transplant setting for patients with myelofibrosis undergoing HCT.

Figure 1

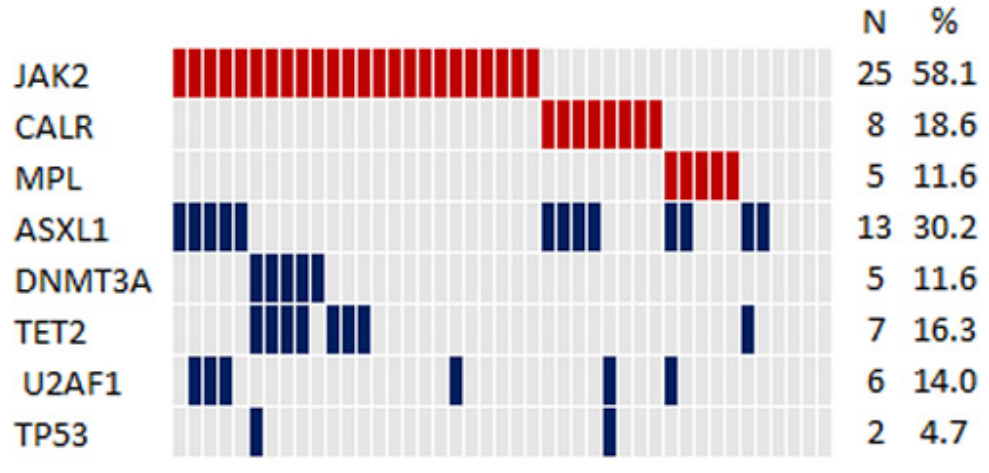

Figure 2