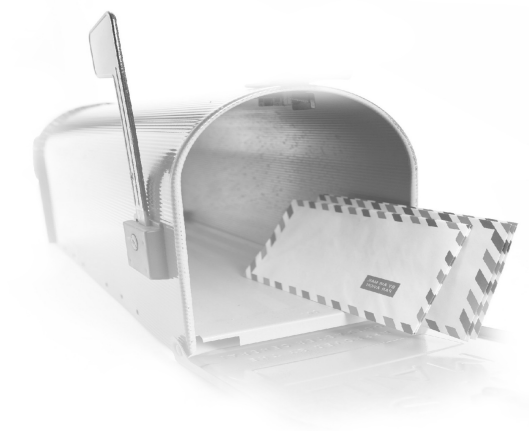

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Letter to the Editor

Ruxolitinib changes the natural course of myelofibrosis and its transplant outcome

THE AUTHOR'S REPLY: In his letter referring to "Will JAK1/2 inhibitors change the standard of care for myelofibrosis (MF)?", Dr. Raut raised two important issues about ruxolitinib: (1) its mechanism of action and (2) its beneficial effect on the outcome of hematopoietic stem cell transplantation (HSCT) in MF patients. The first issue was about how ruxolitinib improved survival without causing any significant effect on disease biology parameters such as the peripheral blast count, marrow fibrosis, cytogenetic response, and *JAK2* V617F allele burden. At the last annual meeting of the American Society of Hematology, long-term outcome data of COMFORT-I and COMFORT-II trials that either showed significantly improved survival of ruxolitinib group compared to placebo (hazard ratio (HR) 0.58, 95% confidence interval (CI) 0.36–0.95) or best supportive care (HR 0.52, 95% CI, 0.27–1.00) were presented. Since peripheral blast counts, marrow fibrosis, and cytogenetics were not investigated in those trials, it is difficult to explain the survival advantage on those parameters. However, with the use of ruxolitinib, the two studies showed significant sustained reduction of the *JAK2* V617F allele burden. In COMFORT-I trials, ruxolitinib resulted in reduction of *JAK2* mutant allele burden by a mean of 10.9% at week 24 ($P<0.0001$) and -21.5% at week 48 ($P<0.0002$) that were independent of baseline *JAK2* V617F levels [1]. COMFORT-II trials also showed significant reduction in allele burden (median reduction rate of -7.0% at 48 weeks and -8.7% at 72 weeks), which was associated with spleen response [2]. Verstovsek *et al.* reported that 50% reduction in palpable spleen length was associated with prolonged survival in ruxolitinib treated patients [3]. These observations suggest that ruxolitinib could alter MF prognosis through reduction of *JAK2* V617F allele burden and spleen volume. However, we should note that survival improvement was not great and longer follow-ups are required. The relationship between *JAK2* V617F allele burden and the survival is also unclear.

The second issue was regarding pre-transplant ruxolitinib and the improvement of HSCT outcome by decreasing proinflammatory cytokines. Several convergent lines of evidence suggested that inflammatory cytokines act as mediators of acute GVHD and cause debilitating symptoms in MF. Ruxolitinib significantly decreased tumor necrosis factor-alpha and interleukin-6 levels for a prolonged time in patients with MF through anti-JAK1-mediated downregulation [1]. In a mouse allogeneic transplant model, ruxolitinib decreased alloreactive CD4+ T cells, expression of CXCR3 in activated T cells and GVHD, leading to improved survival [4]. Poor performance status is associated with poor outcome with HSCT in MF, whereas the reduction in symptomatic burden with JAK1/2 inhibitors may have the potential of improving transplant outcome. Massive splenomegaly is reported to be associated with delayed neutrophil and platelet recovery, suggesting that reduction of spleen volume may induce faster marrow recovery after HSCT [5]. Although these are indirect evidences, they support the suggestion that JAK1/2 inhibitors prior to HSCT may have a beneficial effect on the transplant outcome. Whether pre-transplant JAK1/2 inhibitors decrease GVHD and improve survival in HSCT should be addressed through a prospective trial.

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No potential conflicts of interest relevant to this article

were reported.

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