Is ruxolitinib a potentially useful drug in hematological malignancies with RAS pathway hyperactivation ?

It was with great interest that we read this journal's article by Sachs et al. in which, in a preclinical mouse model, the critical role of Stat5 in the development and maintenance of myeloproliferative neoplasms (NPM) initiated by Nf1-deficiency, has been nicely demonstrated.[1] Since neurofibromin encoded by NF1 is a negative regulator of the RAS signaling pathway, deletion of NF1 leads to hyperactive RAS signaling.[2] Since STAT5 is a downstream effector of JAK2,[3] the authors also investigated the effects of the JAK1/2 inhibitor ruxolitinib in this model. Interestingly, the authors show that attenuation of Stat5 signaling in Nf1-deficient mice, using either a genetic Stat5a/b hypomorphic knock-out or pharmacological Jak2 inhibition by ruxolitinib abrogated MPN, rescued hyperactive signaling pathways, and reversed the expansion of immature myeloid cells.[1] Furthermore, they showed that peripheral blood mononuclear cells (PB MNC) from a patient with activated KRAS juvenile myelomonocytic leukemia (JMML) displayed reduced colony formation in response to JAK2 inhibition by ruxolitinib.[1]

We originally reported that extensive in vitro formation of colony-forming unit-granulocyte-macrophage (CFU-GM) without exogenous growth factors can be found in a subset of patients with chronic myelomonocytic leukemia (CMML).[4] We demonstrated that this spontaneous myeloid colony formation in CMML is a granulocyte/macrophage colony-stimulating factor (GM-CSF)-dependent in vitro phenomenon,[5] and that CMML patients with high spontaneous CFU-GM growth (>100/10^5 PBMNC) have a worse prognosis compared to patients with low CFU-GM growth, suggesting clinical significance of our observation.[6] We have recently demonstrated that high in vitro myeloid colony formation in the absence of exogenous growth factors is highly associated with molecular aberrations in RASopathy genes in CMML patients.[7] We have also reported the in vitro effects of the specific JAK2 inhibitor TG101209 on autonomous CFU-GM formation from PB MNC of CMML patients.[8] TG101209 was found to either block or strongly inhibit spontaneous CFU-GM growth in all 10 patients tested. This inhibitory effect was dose-dependent and significantly more pronounced as compared to the inhibitory effect on stimulated CFU-GM growth from normal individuals. Among the 10 patients included in this study, PB MNC from 6 patients were tested by next-generation sequencing and, in 5 of them, RAS signaling hyperactivation was documented due to mutations in NRAS (n=3) or PTPN11 (n=2), respectively. In a CMML patient with an NRAS mutation, leukocytosis and splenomegaly, who was treated with the JAK1/2 inhibitor ruxolitinib off label, we demonstrated a spleen response and the disappearance of constitutional symptoms associated with a decrease of autonomous CFU-GM formation ex vivo.

These data, along with ours, hence suggest that the inhibition of the JAK2-STAT5 pathway by ruxolitinib may have therapeutic potential, not only in JMML, but also in other RAS-driven hematological malignancies including CMML. This hypothesis seems to be supported by data from a recent multi-institution phase I trial of ruxolitinib in patients with CMML,[9] which showed that splenomegaly, which is commonly associated with RAS pathway hyperactivation,[10] was reduced in 5 of 9 patients by the study drug.

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