Unplugging JAK/STAT in Chronic Myelomonocytic Leukemia

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The proliferative component of chronic myelomonocytic leukemia, related to an increased sensitivity of myeloid progenitors to granulocyte macrophage–colony stimulating factor, suggests dedicated therapeutic approaches. In this issue, ruxolitinib, a JAK1 and -2 inhibitory drug, is shown to induce objective responses in chronic myelomonocytic leukemia patients. Clin Cancer Res; 22(15); 3707–9. © 2016 AACR. See related article by Padron et al., p. 3746

In this issue of Clinical Cancer Research, Padron and colleagues report a phase I trial showing that ruxolitinib, a JAK-1 and -2 inhibitory drug currently approved for patients with severe myelofibrosis, can induce objective responses in patients with chronic myelomonocytic leukemia (CMML; ref. 1). CMML is a clonal malignancy of the hematopoietic stem cell that affects mostly elderly people. This disease has long been associated with myelodysplastic syndromes in clinical trials. The increasing recognition of CMML biologic specificities however suggests specific therapeutic approaches. Accordingly, ruxolitinib was selected following the demonstration that a committed myeloid progenitor population with enhanced sensitivity to granulocyte macrophage–colony stimulating factor (GM-CSF) can be detected in the bone marrow of CMML patients (2).

Fifteen years ago, the World Health Organization (WHO) created a category of overlapping myeloid malignancies that associate dysplastic and proliferative features, of which CMML is the most frequent entity. The myelodysplastic syndrome/myeloproliferative neoplasm category was confirmed in 2008. The main biologic feature of CMML is monocytosis, which can be associated with bone marrow cell dysplasia. The disease diagnosis could be improved by using a multiparametric flow cytometry assay showing an expansion of classical CD14+ CD16 monoocytes over 94% of total monocytes, which rapidly distinguishes CMML from reactive monocytosis, the main confounding diagnosis (3). CMML identification is also supported by the detection of clonal genetic abnormalities. The disease molecular fingerprint associates somatic mutations in TET2 (~60% of cases), SRSF2 (~50%), ASXL1 (~40%), and a signaling gene (~50%). Whole-exome and whole-genome sequencing of peripheral blood monocyte DNA detect a mean number of 14 variants in the coding regions and a mutational signature of ageing, respectively (4). Mutations accumulate almost linearly in the stem cell compartment, and the most mutated cells demonstrate a growth advantage with differentiation (5).

Overall survival of CMML patients is currently approximately 30 months. Allogeneic stem cell transplantation, which is the only potentially curative therapeutic option, is rarely feasible because of age. In other patients, hydroxyurea can be used in proliferative CMML to reduce leukocytosis and spleen size (6). The Federal Drug Administration also approved the use of azacitidine and decitabine in severe CMML. These drugs restore a balanced hematopoiesis in 35% to 40% of them (7). However, they do not significantly reduce the mutated allele burden in leukemic cells, nor do they prevent clonal genetic evolution, ultimately leading to fatal cytopenia or transformation into acute leukemia (5). There is therefore a need for new therapeutic options that would modify the course of the disease.

By pooling CMML with myelodysplastic syndrome in clinical trials, the proliferative component of CMML has long been neglected. Juvenile myelomonocytic leukemia is a rare pediatric myelodysplastic syndrome/myeloproliferative neoplasm sharing various features with CMML. In this disease, monocytosis is related to a constitutive activation of the Ras pathway that induces a specific hypersensitivity of myeloid progenitors to GM-CSF, leading to STAT-5 activation (8). In CMML, such a cytokine-specific hypersensitivity of myeloid progenitors was initially thought to be restricted to a subgroup of patients with mutations in signaling genes (5, 9). By using hematopoietic colony–forming assays and phosphospecific STAT5 flow cytometry, Padron and colleagues demonstrated that hypersensitivity of myeloid progenitors to GM-CSF was measurable in 90% of CMML patients. In response to GM-CSF, the specific α chain and the shared β chain that form the GM-CSF receptor combine into an active heterodimer that interacts with JAK2. The subsequent phosphorylation of JAK2 leads to a specific evoked STAT5 signature that can be used as a read-out of the response to GM-CSF (ref. 8; Fig. 1). Preclinical studies using either an antibody that prevents GM-CSF binding to its cognate receptor or chemical inhibitors of JAK2 supported a role for the GM-CSF/JAK2/STAT5 pathway in the proliferation of CMML myeloid progenitors, providing the rationale for testing JAK2 inhibitors in this disease (2).

The trial reported by Padron and colleagues is a multicentric “rolling six” phase I trial testing ruxolitinib at doses ranging from 5 to 20 mg twice daily. All the 20 enrolled patients had a CMML-1 according to the WHO criteria, indicating that the percentage of
the response to GM-CSF. Upon JAK2 activation, the βc chain becomes phosphorylated and recruits adaptor molecules, leading to the activation of other signaling pathways (gray ovals).

GM-CSF/JAK2/STAT5 pathway. GM-CSF receptor (also known as CD116) is made of a specific α chain subunit (α) encoded by CSF2RA gene and a common β chain (βc) shared with IL3 and IL5 receptors. The GM-CSF hematopoietic growth factor induces the formation of the heterodimeric receptor. In turn, JAK2 is recruited and phosphorylated, which activates several STAT pathways, including STAT5 whose phosphorylation (P) is used in this study as a read-out of the response to GM-CSF. Upon JAK2 activation, the βc chain becomes phosphorylated and recruits adaptor molecules, leading to the activation of other signaling pathways.

References

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