Unplugging JAK/STAT in Chronic Myelomonocytic Leukemia

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Summary

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 janus activated kinase (JAK)-1 and -2 inhibitory drug, is shown to induce objective responses in chronic myelomonocytic leukemia patients.
In this issue of *Clinical Cancer Research*, Eric Padron and colleagues report a phase I trial showing that ruxolitinib, a janus activated kinase (JAK)-1 and -2 inhibitory drug currently approved for patients with severe myelofibrosis, can induce objective responses in patients with a chronic myelomonocytic leukemia (CMML) (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 (MDS) in clinical trials. The increasing recognition of CMML biological 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 MDS/myeloproliferative neoplasm (MPN) category was confirmed in 2008. The main biological 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⁻ monocytes over 94% of total monocytes, which rapidly distinguishes CMML from reactive monocytosis, the main confounding diagnosis (3). CMML identification is supported also 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 ~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 azacytidine and decitabine in severe CMML. These drugs restore a balanced hematopoiesis in 35-40% of them (7). However, they do not significantly reduce the mutated allele burden in leukemic cells, nor 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 MDS in clinical trials, the proliferative component of CMML has long been neglected. Juvenile myelomonocytic leukemia is a rare pediatric MDS/MPN 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 signal...
transducer and activator of transcription (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, Eric 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 alpha-chain and the shared beta 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 (8) (Figure 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 Eric Padron and colleagues is a multicentric “rolling six” phase I trial testing ruxolitinib at doses ranging from 5 to 20 mg BID. All the 20 enrolled patients had a CMML-1 according to the WHO criteria, indicating that the percentage of blast cells in their bone marrow never exceeded 10%. A majority of them had a so-called proliferative CMML, based on their leukocyte count higher than 13 G/L, and eight had been treated previously with a hypomethylating drug. Importantly, ruxolitinib was safe in CMML patients in whom the hematological toxicity described in primary myelofibrosis patients was not observed. The lack of dose-limiting toxicity during the two cycle evaluation period led to recommend a dose of 20 mg BID for the phase 2 trial. Importantly, the peripheral plasma of patients under therapy down-regulates GM-CSF-dependent pSTAT5 in a model cell line, validating the anticipated effect of the treatment. A decrease in the size of the spleen was measured in 5 out of 9 patients with a splenomegaly, hematologic improvement was noticed in 4 cases, and a partial response according to IWG criteria for MDS was observed in one patient.

The pattern of mutations observed in the treated cohort did not strictly reflect the pattern described in larger cohorts of CMML patients. This may be due to the inclusion criteria that excluded those with severe thrombocytopenia, which is often associated with RUNX1 gene mutation, and the preferential enrolment of patients with a proliferative disease. Nevertheless, the observed responses were not restricted to patients with somatic mutations in signaling genes, suggesting that targeting signaling pathways makes senses even in the absence of genetic alteration of these pathways. As in patients with a myelofibrosis, ruxolitinib did not demonstrate a significant impact on mutation allele burden.

Because the MDS criteria are not well appropriate for adult MDS/MPN, an international consortium recently proposed specific response criteria for these diseases (10). The difficulty in capturing the
drug effect on constitutional symptoms by the use of scales that have not been specifically developed for CMML, illustrates the need for more specific response criteria. Importantly, the authors measured an effect of ruxolitinib on bone marrow plasma inflammatory cytokines, which could account for the suspected improvement in B-symptoms, as described in ruxolitinib-treated MPN patients.

The modulation of cytokine secretion as a consequence of JAK1 and JAK2 inhibition in leukemic and surrounding cells could have an impact on the disease course. In a mouse model of chronic myeloid leukemia, inflammatory cytokines control leukemic multipotent progenitor cell fate, thereby promoting leukemia development (11). Conversely, interleukin-10 was proposed to antagonize CMML myeloid progenitor hypersensitivity to GM-CSF (12). Altogether, cytokine synthesis and secretion by cells of the leukemic clone and their environment probably modulate CMML progression and could be therapeutic targets.

Ruxolitinib alone will not cure CMML. Nevertheless, the reported trial demonstrates that targeting the proliferative component of this overlap syndrome could favorably influence the course of the disease. This first biology-driven trial paves the way for testing drug combinations based on the careful investigation of the cell autonomous and non-cell autonomous pathogenic components that generates the CMML phenotype.

References


Figure 1: The GM-CSF/JAK2/STAT5 pathway. GM-CSF receptor (also known as CD116) is made of a specific alpha-chain subunit (α) encoded by CSFR2A gene, and a common beta chain (βc) shared with IL-3 and IL-5 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 is used in the present 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 (gray ovals).
Figure 1:
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