JAK of all trades: Ruxolitinib as a new therapeutic option for CML patients

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Main Text

Chronic myeloid leukemia (CML) is a paradigmatic tumor in oncology research. It was the first cancer in which a recurrent chromosomal abnormality, the Philadelphia chromosome arising from the reciprocal translocation between chromosomes 9 and 22, was identified and subsequently shown to be pathogenic through the production of the fusion oncogene and tyrosine kinase (TK) BCR-ABL. CML also perfectly fits the cancer stem cell model as it arises from a leukemic stem cell (LSC) which represents the reservoir of the disease and, through self-renewal and differentiation, is able to generate the tumor bulk of mature leukemic cells. Finally, the development of BCR-ABL tyrosine kinase inhibitors (TKI) represented the first example of a scientifically validated and highly specific targeted therapy in oncology. Although BCR-ABL TKI have greatly improved patient outcome, with the majority of chronic phase (CP) CML patients achieving deep molecular responses and having life expectancies similar to age-matched population, they are not curative. *BCR-ABL*$^{+}$ LSC and *BCR-ABL* genomic DNA can be detected in patients with undetectable *BCR-ABL* transcript levels in peripheral blood and several clinical studies show that around 50% of the small proportion of patients achieving sustained deep molecular responses will molecularly relapse upon TKI discontinuation. Preclinical studies have shown that CML LSC are resistant to TKI, despite effective BCR-ABL TK inhibition, thus explaining TKI inability to cure CML. This latter observation suggests CML LSC rely on other survival pathways and several putative candidates have been reported as potential therapeutic targets to eradicate LSC and achieve disease cure(1).

Amongst these, the intracellular tyrosine kinase janus kinase (JAK) 2 has been shown to support CML LSC survival, particularly via signal transducer and activator of transcription (STAT) 3 and 5 activation in response to hematopoietic growth factors stimulation, and several preclinical studies have shown that JAK2 inhibitors are able to eliminate CML LSC. This latter

observation coupled with the availability of numerous clinical grade JAK2 inhibitors, currently licensed for the treatment of BCR-ABL$^-$ myeloproliferative neoplasms, has now allowed for the translation of these preclinical findings into a clinical trial in CML patients(2).

In this issue of Leukaemia Research, Sweet and colleagues report the tolerability, safety and preliminary efficacy results of a Phase I clinical trial investigating the combination of the JAK2 inhibitor ruxolitinib with the second generation BCR-ABL TKI nilotinib for 6 months in 11 CP CML patients with evidence of residual disease at molecular level(3). Although the findings of this study need to be interpreted with caution given the small number of patients and the lack of randomized comparison with single agent TKI, the authors report several interesting observations. First, ruxolitinib in combination with nilotinib appears to be well tolerated with no dose-limiting toxicity identified although grade 1/2 anemia was observed in almost 40% of patients, all of which in the cohort treated with highest ruxolitinib dose (i.e. 15mg BD). Second, molecular responses in this small cohort was encouraging with median change in *BCR-ABL* transcripts of 1 log after 6 months of combination treatment. One patient had progressive disease but analysis of the diagnostic material suggested that progression had likely started prior to study entry. Intriguingly, the authors show that the proportion of patients achieving 4.5 log reduction in *BCR-ABL* transcript levels relative to baseline levels, i.e. Molecular Response (MR) 4.5, over 6 months was 40% which is higher than reported in the nilotinib arm of the phase 3 ENESTnd trial, where cumulative rates of MR4.5 over any 6 months period on nilotinib were 5-10%(4). Finally, the authors show that plasma from patients treated with ruxolitinib was able to inhibit STAT3 and 5 phosphorylation in cell lines compared to pretreatment plasma from the same patients, thus providing correlative evidence of the on-target effects of this JAK2 inhibitor.

Several questions however remain to be answered in regards to the efficacy and safety of JAK2 inhibitors in CML patients. Although tolerability of the combination treatment in CP CML patients appears reassuring based on the authors' data, ruxolitinib can cause anemia and more widely cytopenias, as also observed in the study. Given that most CP CML patients on TKI enjoy a near normal quality of life, larger studies will clarify if this therapeutic approach results in increased hematological toxicity which might influence clinicians and patients' decision to use JAK2 inhibitors in this population and limit its use to patients who show no hematological toxicity in response to TKI. Also, as CML LSC resistance mechanisms to TKI are multiple, it will be useful to characterize genetic and transcriptional features of CML LSC from patients at study entry and correlate these features with their outcome to identify predictors of response to this combined approach. These correlative studies might also help to understand if other described mechanism through which JAK2 supports CML LSC survival, such as direct activation of MYC and β-catenin(2), play a role *in vivo* in patients. Finally, it would be tempting to test if such an approach might prove useful in advanced phase/resistant CML. However, given that in advanced phase/resistant disease BCR-ABL TK is often not fully inhibited because of BCR-ABL TK domain mutations, caution should be exercised based on evidence that deletion of *JAK2* might accelerate CML development in mouse models by preferentially causing elimination of normal hematopoietic stem cell compared to CML LSC where BCR-ABL is still active(5).

In conclusion, the work from Sweet and colleagues provides a framework for CML LSC directed clinical trials which could be extended also to other targets identified and validated in preclinical studies, such as EZH2, P53 and MYC(1). More specifically, it represents a springboard for further phase 2 studies testing the role of JAK2 inhibitor in CML, with some already ongoing in other centers (NCT01751425), and ideally comparing in a randomized approach JAK2 plus BCR-ABL inhibitor combination treatment versus single agent TKI as the

authors are planning. These future studies will hopefully confirm the authors' findings, characterize better the mechanisms and predictors of response to JAK2 inhibitors in CML patients and provide a cure for a proportion of the fast-growing CML patient population.

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