Clinical Cancer Research

Aurora Kinase A Inhibition: A Mega-Hit for Myelofibrosis Therapy?

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The positive but limited efficacy of JAK inhibitors has sparked the need for alternative therapeutic targets in the treatment of myelofibrosis. The discovery of novel targets, like Aurora Kinase A, may provide new avenues of single-agent and combinatorial therapy for myelofibrosis and restoration of normal bone marrow function.

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In this issue of *Clinical Cancer Research*, Gangat and colleagues report the results of a phase I clinical trial investigating the effects and safety profile of the highly selective Aurora Kinase A (AURKA) inhibitor, alisertib, in patients with myelofibrosis (1). Accompanying clinical assessment of patient response, they performed a series of *in vitro* experiments at the tissue, cellular, and molecular level to determine the effects of alisertib on bone marrow fibrosis, megakaryocyte morphology, and mutational burden of disease. This phase I study establishes AURKA inhibition as a potentially viable therapeutic option for patients with myelofibrosis, including those who show limited response to previous therapies such as ruxolitinib.

Myelofibrosis, along with essential thrombocythemia and polycythemia vera (which can both progress to myelofibrosis) encompass the Philadelphia chromosome-negative myeloproliferative neoplasms (MPN). Myelofibrosis is characterized by bone marrow fibrosis and atypical clustering megakaryocytes, and is accompanied by splenomegaly and abnormal blood counts. The overwhelming majority of patients with MPN and myelofibrosis carry mutations in *JAK2*, *MPL*, or *CALR*, which all lead to constitutive activation of JAK/STAT signaling and uncontrolled proliferation (2). In addition, a substantial portion of patients ultimately progress to acute myeloid leukemia, drastically decreasing their overall survival. Although still not fully understood, increasing evidence supports the theory of aberrant megakaryocyte function being one of the major drivers of bone marrow fibrosis in patients with myelofibrosis, through irregular cytokine production and alterations in the microenvironment (3, 4).

Abnormal megakaryocyte appearance and function is considered a cellular hallmark of myelofibrosis. Molecularly, impaired megakaryopoiesis observed in myelofibrosis is accompanied by significant reduction of GATA1 expression, implicating the master hematopoietic transcriptional regulator in myelofibrosis pathogenesis (4). GATA1 controls expression of key genes involved in megakaryocyte differentiation and function, and its reduced expression in abnormal megakaryocytes has been observed across patients with myelofibrosis of all mutational backgrounds (*JAK2*, *CALR*, *MPL*; ref. 5). Expression of GATA1 in myelofibrosis progenitors reestablishes a megakaryocyte differentiation program, suggesting a key role for the regulator in normalizing megakaryopoiesis within the diseased state.

The advent of JAK kinase inhibitors, like ruxolitinib, provided the first avenue of targeted therapeutic relief for patients with myelofibrosis. The Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment I and II studies provided overwhelming evidence of the usefulness of ruxolitinib in disease management (6, 7). With alleviation of symptoms and increase in overall survival, ruxolitinib became the first major targeted therapeutic to be used in myelofibrosis. Suppression of JAK/STAT signaling by ruxolitinib in patients has been shown to decrease malignant cell proliferation and reduce symptoms such as splenomegaly, possibly through rapid reduction of inflammatory cytokines (8). However, the effects of ruxolitinib are temporary, with an average duration of response of 2–3 years. Thus, while the direct targeting of aberrant JAK/STAT signaling in myelofibrosis is effective, the identification of novel therapeutic targets is of high importance.

Previous work has implicated AURKA in the pathogenesis of myelofibrosis and acute megakaryocytic leukemia, and has shed light on the mechanisms of its actions within megakaryocytes (9, 10). Its activity is greatly elevated in cells harboring activating JAK/STAT mutations; however, inhibition of AURKA in these cells showed no effect on STAT activity, suggesting AURKA has JAK/STAT-independent effects in the pathogenesis of myelofibrosis. Importantly, unlike suppression of JAK/STAT signaling by ruxolitinib, AURKA inhibition effectively promoted differentiation and polyploidy within megakaryocytes, and loss of a single AURKA allele was sufficient to prevent the myelofibrosis phenotype *in vivo* (9). Consequently, AURKA inhibition has become an attractive target for the restoration of normal megakaryocytic function within the setting of myelofibrosis. Alisertib, a potent and selective AURKA inhibitor, has been previously evaluated at the preclinical state *in vitro* and in mouse models harboring the *JAK2V617F* and *MPLW515L* mutations that mimic the common

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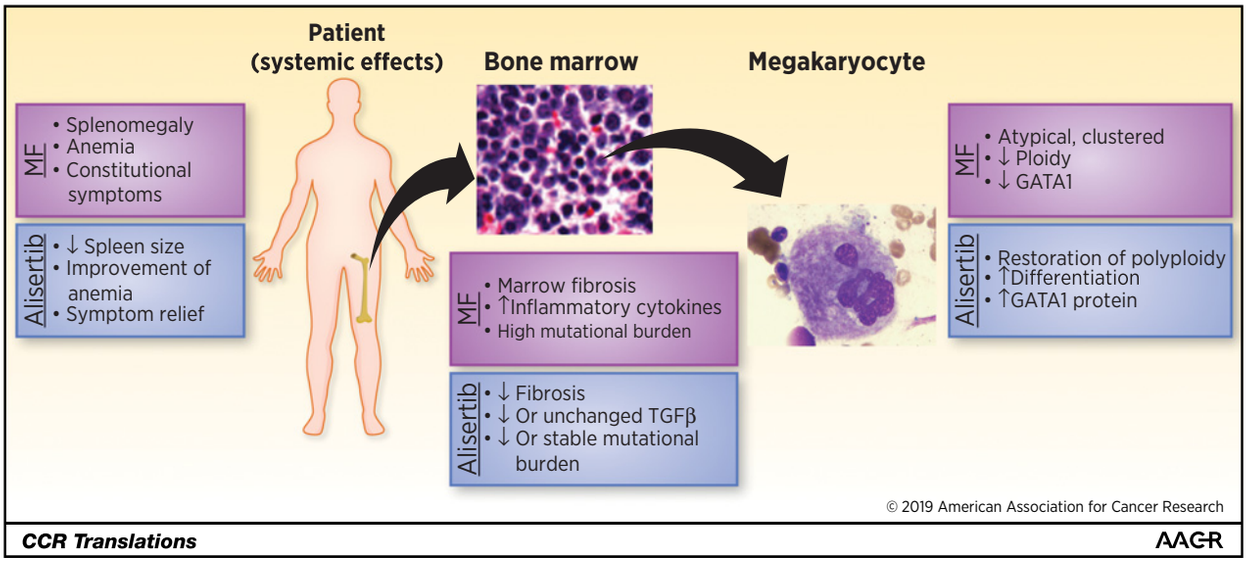

Figure 1.

Observed effects of alisertib on the clinical and molecular manifestations of myelofibrosis (MF). Alisertib treatment in patients with myelofibrosis had positive outcomes at the systemic, tissue, and cellular level. Along with partial mitigations of splenomegaly, anemia, and symptomatic relief, alisertib decreased detectable fibrosis and reestablished normal megakaryocyte function. AURKA inhibition also restored GATA1 function and decreased or stabilized the variable allele frequency of detectable pathogenic mutations (bone marrow and megakaryocyte images used under license from Shutterstock.com).

mutations seen in patients (9). These results provided impetus for the investigation of alisertib in safely treating myelofibrosis in the clinical setting.

The authors first established safety and tolerance of alisertib in the 24 enrolled patients in this trial, noting grade 1 or 2 adverse effects (including diarrhea, nausea, alopecia, and fatigue) in some patients; the major grade 3 or 4 adverse effect was cytopenia, as the authors predicted. After assessing the safety of alisertib in patients with myelofibrosis, the authors then evaluated patient response and the cellular and molecular consequences of AURKA inhibition. With the majority of patients carrying *JAK2*, *CALR*, or *MPL* mutations, and with 63% of patients having prior treatment with JAK inhibitors, the authors set out to test AURKA inhibition as a therapeutic target in myelofibrosis, with potential JAK/STAT-independent effects that provided key and distinct clinical benefits at the symptomatic, tissue, and cellular level.

Overall, the authors observed a nearly 30% response rate with respect to both reduction in splenomegaly and symptom burden. Of those that continued through at least six cycles of therapy, nearly half of patients showed promising symptom response and reduction in splenomegaly. Unlike the previously observed effects of ruxolitinib, the reduction in spleen size in alisertib-treated patients was not accompanied by consistently reduced inflammatory cytokines, suggesting therapeutic response may occur through a mechanism distinct from ruxolitinib. At the tissue and molecular level, alisertib relieved bone marrow fibrosis and improved GATA1 detection in the majority of samples analyzed. These results further implicate AURKA activity in the promotion of myelofibrosis and abnormal megakaryopoiesis, and demonstrate that its inhibition provides therapeutic benefit.

In summary, this phase I clinical trial evaluating the safety and efficacy of AURKA inhibition by alisertib has revealed a promising new avenue in myelofibrosis therapy. As summarized in Fig. 1, the authors found positive effects of alisertib on marrow fibrosis, splenomegaly, and anemia. They also elegantly demonstrated the restoration of normal megakaryocytes at the cellular and molecular level through analysis of polyploidy, differentiation, and GATA1 expression. In addition, alisertib ably reduced the allelic burden of *bona fide* myelofibrosis mutations (i.e., *JAK2*, *MPL*, and *CALR*) in half of the patients analyzed. In sum, Gangat and colleagues have shown the safety of alisertib in myelofibrosis and have demonstrated clinical activity in many patients within this trial. With positive clinical outcomes in a substantial amount of patients, and deep insight into the mechanism of action at the cellular level within megakaryocytes, the authors of this study have revealed a much needed novel target for the treatment of myelofibrosis, and have set the foundation and rationale for further testing of alisertib as a single-agent and combinatorial therapeutic in myelofibrosis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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