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Improvement of bone marrow fibrosis with ruxolitinib: will this finding change our perception of the drug?

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Ruxolitinib, a JAK1 and JAK2 inhibitor, has been tested and approved for the treatment of primary and secondary myelofibrosis. Reduction of spleen volume and improvement of constitutional symptoms and quality of life have been reported as the major findings in sponsored randomized clinical trials. Recent data indicated that the drug improves bone marrow fibrosis and that different targets may be involved in this response. These new data, which require confirmation in prospective trials, may change our perspectives and therapeutic strategies for this disease.

Ruxolitinib (Jakavi), a JAK1 and JAK2 inhibitor, was recently approved for the treatment of patients with primary or secondary myelofibrosis. Approval was based on the results of COMFORT studies that tested the drug versus placebo and best supportive care, and showed achievement of primary endpoint (reduction of more than 35% of spleen volume from baseline) and improvement of constitutional symptoms and quality of life [1,2]. Preliminary results on improvement of fibrosis were also published. MD Anderson Cancer Center reported the preliminary results of a Phase I/II, single-arm study in which 158 patients had been enrolled with primary or secondary myelofibrosis that was treated with ruxolitinib. Bone marrow (BM) biopsies were performed at baseline and at 24 and 48 months. Overall, 68 patients were eligible for this exploratory analysis and 18 patients had a biopsy at 48 months. Three independent hemopathologists reviewed all samples for the grade of fibrosis according to WHO classification, the degree of collagen and osteosclerosis according to international consensus criteria. Improvement of fibrosis was independent of the splenic response and, overall, at 24 months, 15% of patients had an amelioration of fibrosis compared to 6% of patients treated with conventional therapy, 57% showed stabilization and 37% had a worsening of fibrosis (as compared to 62 and 54% of patients, respectively, treated with best available therapy). Among the patients evaluable at 48 months, the rate of improvement reached 22% (as compared to 2% for patients on conventional therapy). The cumulative risk of death over time was 15% for patients who had a worsening of fibrosis as compared to less than 10% for patients who showed improvement of fibrosis at 36 months [3].

A single case was reported by Wilkins *et al.* [4]: a 74-year-old male patient with secondary myelofibrosis after a previous diagnosis of polycythemia vera, with an International Prognostic Scoring System (IPSS) intermediate-2 risk. The patient was started on ruxolitinib at a dose of 15 mg two-times a day (b.i.d.) and showed a dramatic reduction of splenomegaly. After the dose was reduced to 10 mg b.i.d. for thrombocytopenia, splenomegaly resolved completely. At baseline, he was classified as having a fibrosis score 3 according to WHO classification: after 48 weeks of treatment, reticulin fibers were less prominent and after 168 weeks, they were completely absent with normal cellularity. In this case, a reduction of JAK2 allelic burden was also reported. Another case was

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described by our group: a 52-year-old male diagnosed as having secondary myelofibrosis IPSS intermediate-2 risk after a polycythemia vera. At baseline, fibrosis score 3 was documented; treatment with ruxolitinib at a dose of 20 mg b.i.d. was well tolerated without side effects. After 4 weeks from the start of treatment, the patient showed a marked improvement of the constitutional symptoms, especially night sweats and abdominal discomfort, and about 40% reduction in palpable spleen longitudinal diameter (8 cm below the costal margin) was observed. At week 50 from the start of ruxolitinib, the patient achieved the best response with no palpable spleen at clinical examination. After 17 months of therapy, a BM biopsy was performed, which documented a complete resolution of fibrosis [5]. Recently, the third case was reported by Al-Ali *et al.*: a 50-year-old male was enrolled in the COMFORT-II study and treated with 25 mg b.i.d. of ruxolitinib without toxicity. Histologic improvement in marrow cellularity, megakaryocytic and granulocytic lineages was first evident at week 126 with further reversal of myelofibrosis-related abnormalities including marrow fibrosis observed by week 216 [6].

In the COMFORT-II study, 138 patients had assessment of BM fibrosis at baseline and 96 patients had at least one follow-up assessment. Improvement in marrow fibrosis was seen in 21% of patients treated with ruxolitinib in the COMFORT-II study, whereas the condition of 39% of patients worsened. A complete resolution of BM fibrosis was observed in four patients, as compared to none in the best available therapy arm [2].

At present, only allogeneic stem cell transplant represents the treatment option with curative potentiality and resolution of BM fibrosis in myelofibrosis [7]. There have been occasional reports also with interferon, either in patients with other myeloproliferative disorders or in early primary myelofibrosis [8,9]. The pathogenesis of fibrosis in myelofibrosis is suggested to be polyclonal and the stromal reaction appears to be secondary to the production of growth factors including TGF-β, PDGF-β, β-FGF, VEGF, EGF and PF-4 by hematopoietic cells and megakaryocytes from the malignant clone [10]. All these cytokines are also mediators of fibroblast and endothelial cell proliferation, suggesting a connection between fibrosis and angiogenesis. In particular, several groups have studied the role of PDGFR and TGF-β: the latter has a pathogenetic relevance in increased biosynthesis of type I, III and IV collagens and fibronectin and in blocking matrix degradation by reducing collagenase-like protease synthesis and enhancing protease inhibitor expression. Also, β-FGF, a potent angiogenic factor, acts as a modulator of fibroblast function, IL-1, serum amyloid P and calmodulin, and VEGF has been reported to be higher in the plasma of patients affected by myelofibrosis, as reviewed in [10]. Ruxolitinib has been reported to have an effect on the production of several pro-inflammatory cytokines: probably in some patients, this reduction could improve the progression of fibrosis. Recent data correlated the grade of BM fibrosis with the frequency of CD68 and CD168+ macrophages and mast cells. Out of 63 patients studied, 14.3% showed an improvement in BM fibrosis after ruxolitinib treatment, which induced in 48.3% of cases a significant decrease in the overall amount of CD68+ macrophages and modulation of CD163, a scavenger receptor upregulated by these cells. In this cohort, a significant reduction in the expression of associated cytokines such as TNF-α and macrophage inflammatory protein-1α was observed, both at 4 weeks and 24 months [11]. Ruxolitinib was also implicated in the reduction of microvascular density and microvessel area: in patients who showed an improvement of BM fibrosis, a significant reduction of VEGF expression was also detected at 24 months, together with a reduction of CD34+ hematopoietic progenitor cells, but without complete eradication of stem cells [12]. In the same cohort of patients, Kvasnicka *et al.* also reported ruxolitinib-induced modulation of BM microenvironment with decrease of plasma cells in 70%, reduction of megakaryocytes frequency in 52% and of atypia in 37% of analyzed patients. Serum levels of 73 cytokines were studied and 10 cytokines, which were C-reactive protein, IL-10, macrophage-derived cytokine, stem cell factor, TNF-α, apolipoprotein A1, eotaxin, haptoglobin, immunoglobulin E and tissue inhibitor of metalloproteinase-1, were identified that strongly correlated with morphologic changes [13].

The fact that the drug can have an important action on the cytokine level, modulation of microenvironment, and decrease of hematopoietic progenitors and, consequently, on the progression of fibrosis, apparently independent of JAK2 inhibition, may change our approach on therapeutic strategies for this disease. All these clinical and biological data should be confirmed prospectively in a large cohort of patients treated outside clinical trials, in order to validate these results. If the drug is able to reduce fibrosis and $CD34^+$ stem cells, it is possible to hypothesize that ruxolitinib could also be used in patients with early stage myelofibrosis in an attempt to change the clinical course of their disease. Further prospective trials should be planned as soon as possible to answer these questions.

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