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Myelofibrosis (MF), either primary or secondary to polycythaemia vera or essential thrombocythaemia, is the most symptomatic and has the worst prognosis among the *BCR-ABL1*-negative myeloproliferative neoplasms (MPN). Most recent estimates of median survival range from 6–7 years, comparable to those of other haematologic malignancies, such as some chronic lymphoproliferative malignancies.[1] Patients with MF fall along a spectrum that ranges from those who are fully asymptomatic to those who have severe symptoms that affect patients' quality of life. Another characteristic of MF is that the disease is associated with progressive constitutional symptoms, increasing splenomegaly and worsening cytopenias, and increasing risk of leukaemic transformation.

MF mostly affects elderly people, the median age at diagnosis being >60 years, but there are rare cases of asymptomatic young people with a diagnosis of MF; in these cases, allotransplantation of haematopoietic stem cells is the only therapeutic method with curative intent. The clinical landscape is very diverse, with spleen enlargement, due to extramedullary haematopoiesis, and portal hypertension being responsible for abdominal discomfort, early satiety, and abdominal pain. Anaemia and constitutional symptoms can accompany MF, with fatigue the most often seen symptom. Some patients may report other symptoms. To have a more objective evaluation of the symptoms, several symptom scores have been developed. In daily clinical practice, most used is the Myeloproliferative Neoplasm-Symptom Assessment Form (MPN-SAF), which assesses 10 symptoms: fatigue, inactivity, night sweats, itching, fever, weight loss, bone pain, early satiety, problems with concentration, and abdominal discomfort.[2] This is a very useful tool to evaluate the burden of the disease dynamics. Quality of life in patients with MF is severely compromised by several constitutional symptoms (i.e. fatigue, night sweats, fever, weight loss), pruritus, and symptoms from frequently massive hepatosplenomegaly.

For MF diagnosis, we are using World Health Organization (WHO) criteria in clinical practice, which incorporates all the progress made in recent years regarding the mutational status, but also includes histological bone marrow (BM) patterns which differentiate fibrotic primary MF (PMF) from early/prefibrotic PMF.[3] The interpretation of BM histopathology features, as required by the current WHO classification, requires experienced pathologists.[1] This update of WHO criteria will probably be expected, in the future, to improve distinction of the different MPN subtypes by the histological BM patterns and corresponding clinical features.

Our understanding of MF has continuously evolved in the last decade. Numerous Janus Kinase 2 (*JAK2*) mutations and deletions are implicated in MPN; dysregulated JAK-STAT signalling plays an important role in MF disease pathology. Discovery of the Val617Phe mutation of the *JAK2* gene in 2005[4] in the majority of MF patients represented an important step towards elucidating the pathogenesis of this disease. Mutations in the thrombopoietin receptor gene (*MPL*) were subsequently found in a smaller percentage, followed, in recent years, by the discovery of mutations in the calreticulin gene (*CALR*) which have been observed in a proportion similar to Val617Phe mutation.[5] A smaller part of patients have 'triple negative' disease, which has been associated with inferior outcomes.[5] In recent years, other mutations (*ASXL1*, *SRSF2*, *IDH1/2*) associated with lower overall survival or leukaemia-free survival were described. The study of new mutations in recent

years, together with the already known prognostic scores, measured through the International Prognostic Scoring System (IPSS) used at diagnosis (which stratifies the patients into four risk groups: low and intermediate-1 groups have a longer survival compared to intermediate-2 or high-risk groups), and the Dynamic International Prognostic Scoring System (DIPSS) used in dynamics over the course of the disease, help us to have an idea about the future evolution of MF.

HOW I TREAT MYELOFIBROSIS

The main goals of therapy for PMF are the prolongation of survival and, if possible, also cure, which is currently achieved only by allogeneic stem cell transplantation (allo-SCT), but, due to its increased risks, morbidity, and mortality, it is usually restricted to eligible high and intermediate-2-risk MF patients. If prolongation of survival or cure is not possible, symptom-orientated palliation and quality of life become the primary goals of therapy. Besides the paramount progress in the biology of the disease, many efforts have been directed toward the development of molecularly targeted therapies, including inhibitors of JAK1 and JAK2. The international guidelines for MF, including those from the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO), were updated and reflect the changes in the therapeutic area; however, the incorporation of new WHO diagnosis criteria are still required.

For low-risk and asymptomatic patients, the 'watch-and-wait' approach is still used, with careful monitoring of the patient to ensure initiation of the therapy as soon as the patient status changes. For intermediate and high-risk patients with symptomatic splenomegaly and MF-related symptoms, hydroxyurea was the most used cytoreductive drug in the past; surgery and radiation therapy were used for splenomegaly, but are associated with significant morbidity and mortality. For patients with MF and anaemia, specific drugs are used to improve haemoglobin levels: erythropoiesis-stimulating agents, androgens, or immunomodulatory agents, but the results are usually temporary and sometimes incur severe side effects, and limited availability can restrict their use. Blood transfusion can be an option to raise haemoglobin levels for some cases.

Among JAK inhibitors, several molecules are still in different phases of development. The differences in their toxicity profile and efficacy that have been reported in clinical trials suggest variability of these molecules regarding potency and target selectivity.

The only approved JAK inhibitor for splenomegaly or symptoms of MF is ruxolitinib, approved by European Medicines Agency (EMA) in 2012,[6] irrespective of the risk group or by presence of *JAK* Val617Phe mutation. Ruxolitinib is indicated for MF in adult patients who have splenomegaly or symptoms related to the disease, such as fever, night sweats, bone pain, and weight loss. It has been shown to be highly effective in ameliorating disease symptoms and reducing spleen size. In the COMFORT I pivotal study, as well as in the COMFORT II study, the primary endpoint of obtaining >35% reduction in spleen volume by imaging techniques at 24 or 48 weeks of treatment was achieved, with ruxolitinib improving overall survival versus placebo or best available therapy.[7,8] The starting dose of ruxolitinib depends on platelet count, but the dose should be titrated up as soon as possible to get the best spleen response to treatment. Even though anaemia may initially worsen during ruxolitinib treatment, the haemoglobin levels tend to improve over time, but, in rare cases, anaemia represents the reason for ruxolitinib discontinuation.[7,8] In daily practice, for some MF patients, the improvement of symptoms can minimise the impact of anaemia. The most common haematological side effects are anaemia and thrombocytopenia, which are manageable. The response to treatment with ruxolitinib in MF is illustrated by the results of the COMFORT studies, showing an improvement in overall survival, and it is therefore the best available therapy for the moment.

Despite the recent developments in understanding the molecular biology of MF and treatment with JAK inhibitors, which have shown significant clinical benefits for the patients, there remains an unmet need for the condition, due to its molecular and clinical heterogeneity with high degrees of variability from patient to patient; more research is needed to standardise or to apply a personalised approach to every patient based on molecular biomarkers.

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