Manejo terapeutico de los sindromes mieloproliferativos Phi negativos

Management of ET, PV, MF: a practical approach and future directions

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For years, only few cytotoxic drugs like hydroxyurea (HU), busulfan, and pipobroman were available to treat Philadelphia-negative myeloproliferative neoplasms (MPNs), including polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF).[1] However, our knowledge of the pathophysiology of these disorders has considerably changed with the identification of deregulated signaling pathways like the JAK/STAT pathway, or mutations affecting the epigenome.[2] Indeed, MPNs have entered into a new era of targeted therapy, opened with the approval of the first-in-class JAK inhibitor, ruxolitinib, in myelofibrosis (MF)[3, 4] and polycythemia vera (PV).[5]

With conventional therapies, treatment of MPNs primarily aims at reducing the risk of vascular events, which are the main causes of mortality and morbidity at diagnosis and during the first years of follow-up.[6] However, transformation to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) become major concerns after 15 to 20 years of evolution.[7] The development of new therapies raises the hope of new objectives including reduction of the long-term risk of transformation to MDS or AML, achievement of molecular or histopathological complete remissions, and possibly cure. However, to date, only allogeneic hematopoietic stem cell transplantation (ASCT) can cure selected patients with high-risk MF.

Vascular risk assessment

Although many risk factors for vascular complications have been assessed and have been found to have some relevance in retrospective studies, the most reliable parameters remain very easy to collect: age and history of vascular events. Patients younger than 60 years and without any previous thrombosis or bleeding are at low risk of developing vascular

complications. In contrast, patients with one or both these features are at high vascular risk and will benefit of cytoreductive therapy.

In PMF, the overall median survival being around 6 years, the relevant end point for prognostication is survival. The International Prognostic Scoring System (IPSS)[8] is used at diagnosis to distinguish four risk categories (low, intermediate-1, intermediate-2 and high risk). This system has been further refined by the development of the "dynamic" IPSS (DIPSS)[9], which may be used at any time during follow-up, and the "DIPSS-plus" score[10] that incorporates thrombocytopenia, transfusion requirements and cytogenetics. The role of *CALR*[11, 12] and other mutations (i.e.*EZH2, ASXL1, SRSF2, IDH1/2* mutations), comprising a high-molecular risk category in PMF[13], has been underscored but has yet to be incorporated in a new prognostic model.

Treatment of polycythemia vera

General cardiovascular risk factors (smoking, hypertension, diabetes, dyslipidemia…) should not be neglected and require a particularly careful evaluation in PV patients since thrombosis is often multifactorial.

Phlebotomy can be an emergency therapy at diagnosis, in patients presenting with very high hematocrit and clinical signs of hyperviscosity, as well as a long-term maintenance therapy to control the hematocrit in low risk patients.[14] A recent multicenter, randomized clinical trial (Cyto-PV) showed that an hematocrit maintained strictly below 45% during follow-up was significantly associated with a lower incidence of thrombosis[14].

Low-dose aspirin is the second cornerstone of PV therapy since it has been shown in the ECLAP study to significantly reduce a primary combined end point including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and major venous thromboembolism[6].

In addition to this strategy, a cytoreductive drug should be prescribed in high-risk PV patients. The European LeukemiaNet (ELN) recommendations suggested that hydroxyurea and interferon-alpha (IFN-α) were the cytoreductive treatments of choice as first-line therapy for high-risk PV[1]. HU is a well-known drug, with good efficacy and tolerance in the majority of patients. However, skin toxicity and secondary resistance may develop over time leading to treatment discontinuation in 10-20% of patients.[5] Another issue for PV patients in the very long term is the risk of disease transformation[7]. Overall, there is no definitive evidence for (or against) a leukemogenic risk of HU. Thus, it seems reasonable to adopt a conservative approach and to consider alternative treatments in young subjects, and in those previously treated with other myelosuppressive agents.

IFN-α has been shown to induce a high rate of hematological response and to significantly reduce the malignant clone as shown by the percentage of *JAK2*V617F mutated allele. In selected patients, complete hematological, molecular and histopathological remissions were observed, suggesting a possible impact on disease natural history. Main toxicity and contra-indications for IFN-α are well known since the wide use of this drug in viral hepatitis patients.[15] However, this drug is not approved for the treatment of PV.

The choice of second-line myelosuppressive drugs for PV should be carefully evaluated because some drugs administered after HU may enhance the risk of AML. Therefore, one may switch drugs between HU or IFN-α

Very recently, ruxolitinib was evaluated in PV patients intolerant of or resistant to HU in a phase 3 randomized trial versus best available therapy (BAT).(5) The primary endpoint (a composite of hematocrit control and a ≥35% reduction in spleen volume) was met by 21% of patients in the ruxolitinib arm versus 1% in the standard therapy arm. In addition, a greater proportion of patients receiving ruxolitinib achieved complete hematologic remission and experienced a significantly better improvement of PV-related symptoms. The most frequent grade 3 or 4 adverse events reported by patients receiving ruxolitinib were thrombocytopenia (5.5%), dyspnea (2.7%), anemia (1.8%), and asthenia (1.8%). Other adverse events of interest included herpes zoster infection, which was observed in 6.4% of patients in the ruxolitinib arm (all grade 1 or 2), and non-melanoma skin cancer (NMSC) that occurred in 4 (3.6%) patients. Based on the results of this study, ruxolitinib was recently approved by the FDA and the EMA for the treatment of patients with PV who have had an inadequate response to or are intolerant of HU, and is a clear new option for second line therapy in these patients.

Treatment of essential thrombocythemia

In contrast with PV, the potential benefit of aspirin therapy has never been assessed in a randomized controlled trial in ET. In addition, there is a concern that bleeding is a particular risk for ET patients with extreme thrombocytosis (>1,500x10^9/L) due to an acquired von Willebrand disease. Considering these uncertainties, low-dose aspirin remains rec-

ommended for high-risk ET patients without a clear contraindication to this drug.[1] On the other hand, the presence of extreme thrombocytosis (>1.500x10^9/L) temporarily contra-indicates the use of antiplatelet agents, a therapy that can be started after reduction of the platelet count with cytoreductive drugs.
Regarding the choice of the first-line cytoreductive therapy for high-risk ET patients, recommendations can be based on 3 randomized trials.[16-18] HU versus no myelosuppressive therapy significantly reduced the rate of thrombosis in high-risk ET patients[16], showing that these patients should receive a cytoreductive drug and not only antiplatelet agents. The use of anagrelide versus HU has been evaluated in two studies: the PT-1 study and the non-inferiority ANAHYDRET study. Based on these results, HU and low-dose aspirin is often the recommended first-line therapy for high-risk ET,[1] but anagrelide may also be appropriate in specific subgroups of patients. The role of IFN-α therapy in ET needs to be clarified, although many small phase 2 studies have shown that this drug was also very efficient to control thrombocytosis.[15] In addition, it has also been shown that IFN-α was able to induce molecular responses by reducing the mutant allele burden in patients harboring mutations in *JAK2*[19] or in *CALR*[20] genes. The use of cytotoxic agents, in the youngest and/or especially in combination, should be avoided where possible, and IFN-α or anagrelide could be the best options in these situations.

Treatment of myelofibrosis
Since there is no curative therapy other than ASCT for myelofibrosis, treatment is basically palliative and usually guided by the principal disease manifestation.
Anemia: Of note, no drug has approval for this particular indication. One option is the use of erythropoiesis-stimulating agents (ESA), which have been reported to improve anemia in 25%-50% of patients[21]. Androgens have also been reported to improve anemia in a similar proportion of patients. Immunomodulating agents may also be useful in managing MF-related anemia. Low-dose thalidomide or low-dose lenalidomide, combined for the induction treatment with prednisone, provide a 20%-30% response. Of note, lenalidomide as a single agent is the treatment of choice for MF patients with 5q deletion.[22] Corticosteroids alone may sometimes be helpful and provide modest benefit for patients, especially if a hemolytic part can be demonstrated. Lastly, splenectomy can be useful in patients with transfusion-dependent anemia refractory to any therapy, but needs careful evaluation due to the risks of complication.

Splenomegaly: HU used to be the first-line therapy for symptomatic splenomegaly, about 40% of patients experiencing a reduction in spleen size. However, HU efficacy is usually modest and not durable and is currently clearly superseded by JAK inhibitors in this indication (see below). Splenectomy is sometimes required in patients with large and painful splenomegaly refractory to medical therapy. Splenectomy requires an experienced surgical team and critical care support to minimize the risks associated with the procedure, since mortality and morbity rates of 5-10%, and 25%, respectively, have been reported[23]. Splenic irradiation is another alternative treatment of refractory and symptomatic splenomegaly. However, this treatment should be used with caution (fractionated, low dose) due to a high risk of severe cytopenias.

The role of JAK inhibitors: To date, only ruxolitinib, the first in-class oral JAK1/JAK2 inhibitor, was approved for MF treatment. Two independent phase 3 studies have shown a significant efficacy of ruxolitinib to reduce splenomegaly and improve symptoms compared to placebo (COMFORT-1 study)[4] or best available therapy (COMFORT-2 study)[3]. Thrombocytopenia is a frequent adverse event observed with ruxolitinib (contra-indicated in patients with platelets lower than 50 x 10^9/L), requiring dose adaptation but very rarely drug discontinuation. New onset or worsening of anemia can also be anticipated when starting ruxolitinib therapy, especially during the first three to six months of therapy. This drugs is also associated with an increased risk of infection, requiring patients' information and sometimes prophylactic measures[24].
A survival advantage for patients treated with ruxolitinib was found in the phase III studies. However, there is still little evidence of a disease modifying effect, although case reports suggest that reduction in JAK2 mutant allele burden and bone marrow fibrosis can be achieved with long term use of ruxolitinib in selected patients.
Among other JAK inhibitors currently tested in phase 3 studies, pacritinib may have the peculiarity of a lack of toxicity on the megakaryocytic lineage allowing its use in thrombocytopenic patients.[25]

Momelotinib, despite its potent anti-JAK2 activity, may have a positive impact on the anemia of transfusion-dependent patients.[26]

The role of stem cell transplantation for myelofibrosis in the era of JAK inhibitors: ASCT currently remains the only curative treatment approach for myelofibrosis, resulting in resolution of bone marrow fibrosis, molecular remission and restoration of non malignant hematopoiesis[27]. However, transplant related mortality is not negligible justifying careful patient selection. The best candidates for ASCT are patients with high risk MF (intermediate-2 and high-risk categories according to IPSS), the limit of age being discussed according to conditioning intensity. The use of ruxolitinib before transplantation is evaluated in prospective studies, and should therefore presently be considered as experimental.

The future of MPN therapy

One possible avenue for MPN therapy is the development of personalized medicine. Indeed, among cancers, MPNs could be ideal candidates for such strategy. There is evidence showing that the mutational profile found in patients' hematopoietic cells has an influence on treatment efficacy. In PV, IFN-α has a differential impact on malignant clones according to the presence of *JAK2* or *TET2* mutations, the *JAK2*-mutated clones being much more sensitive to IFN-α than clones with *TET2* mutation.[28] These findings suggest that the mutational profile could provide important information for the choice of therapy. This could be particularly important in patients with MF, since they have the poorer life expectancy and often complex mutational profiles.

In terms of new therapies, two classes of drugs are currently evaluated in early phase studies and may play a role in MPN management in the future. First, histone deacetylase inhibitors have shown some efficacy, like panobinostat in PMF[29] or givinostat in PV[30]. Most promising results with these drugs may result from combination with JAK inhibitors by targeting parallel signaling pathways involved in disease development. A telomerase inhibitor, imetelstat, has also been shown to have efficacy in ET and PMF, and is currently evaluated for efficacy and safety.[31]

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