Myeloproliferative neoplasms and personalized medicine: the perfect match?

Jean-Jacques Kiladjian,[1,2] and Claire Harrison[3]

[1]Hopital Saint-Louis, APHP, Centre d'Investigations Cliniques, Paris France; [2]INSERM UMR-S 1131, Institut Universitaire d'Hématologie, Université Paris Diderot, France; [3]Guy's and St Thomas' NHS Foundation Trust, London, UK.

E-mail: jean-jacques.kiladjian@sls.aphp.fr *doi:10.3324/haematol.2015.137182*

For decades the Philadelphia-negative myeloproliferative neoplasms (MPNs) have been treated with a handful of non-specific cytoreductive drugs like hydroxyurea (HU), pipobroman, or busulfan.[1] Anagrelide, with its specific action on thrombocytosis, and interferon alpha (IFNa) opened new perspectives for a more personalized approach. For example, the PT-1 study showed for the first time in MPNs that molecular lesions could have an impact on response to therapy.[2] In that randomized study, patients with essential thrombocythemia (ET) and *JAK2V617F* mutation had better outcomes when treated with HU compared to anagrelide, a difference that was not significant in patients without the mutation.[3] In addition to this possible difference in terms of clinical and hematologic response to a given drug, the introduction of biomarkers in cancer management also reached the MPN area, initially in chronic myeloid leukemia (CML) where *BCR-ABL1* is now a clear marker of treatment efficacy.[4,5] In classical MPNs, first possible evidence for such a biomarker came from studies with IFNa showing that this drug could drastically reduce *JAK2V617F* mutant clones, an effect that can be monitored in peripheral blood by quantification of the mutant allele burden over time.[6] However, response to IFNa may depend on the mutations found in the MPN clones, since it was also shown that clones harboring mutations in the *TET2* gene could be less sensitive to this drug than *JAK2*-mutated clones.[7] Among MPNs, myelofibrosis is the disease with usually more complex mutational patterns, patients often harboring more than one mutation.[8] Indeed, previous studies showed that some mutations (in *ASXL1*, *EZH2*, *SRSF2*, *IDH1-2* genes for example) conferred a high risk of poor outcome.[9] The next step for development of personalized medicine in MPNs will, therefore, probably come from the development of next generation sequencing (NGS) techniques. When widely available (and if affordable), NGS will allow for the precise determination of molecular patterns of patients with MPNs.[10] These new data will hopefully help performing prospective validation of the prognostic and therapeutic impact of molecular lesions. Indeed, such data may also allow us to reclassify the individual subcategories of diseases since currently our diagnostic categories and treatment targets are also still based upon clinical descriptions of entities described over a century ago.[11-13] One could argue perhaps that more progress has been made in the rarer MPN entities such as the chronic eosinophilias and recently chronic neutrophilic leukemia, where the entities have been identified on a molecular basis and targeted treatment, e.g. with *BCR/ABL* kinase inhibitors or, recently, ruxolitinib for *CSF3R* mutation positive chronic neutrophilic leukemias.[14,15]

However, personalization of MPN therapy could also rely on tools other than molecular techniques. Another possible clue to help in the treatment choice in ET, for example, could be bone marrow morphology. After PT-1, a second randomized study compared HU and anagrelide in high-risk ET patients, the Anahydret study.[16] One of several differences with PT-1 consisted of the diagnostic criteria used for ET: WHO in Anahydret *versus* PVSG criteria in PT-1. This difference probably explains in part the different conclusions of these two studies (non-inferiority of anagrelide in Anahydret, compared to superiority of HU in PT-1). Whatever the possible debate about these results, one can consider that it could be possible to determine a profile of ET patients more likely to clearly benefit from HU, e.g. having the *JAK2V617F* mutation, more predisposition to arterial events, some degree of fibrosis in the bone marrow, etc. Or, indeed more radically as alluded to earlier, we could completely reclassify these diseases using scientifically robust tools into specific "personalized" categories.

In addition to these current attempts to better classify patients in order to better tailor their therapy, the discovery of the *JAK2V617F* mutation in MPNs also prompted the development of so-called targeted therapy, i.e. firstly intensive clinical research using JAK inhibitors. These clinical studies led to the approval of the top-of-the-class JAK1-JAK2 inhibitor, ruxolitinib, in myelofibrosis and, more recently, for the treatment of PV patients resistant to or intolerant of HU.[17-19] Other JAK inhibitors are currently evaluated in phase III studies, like pacritinib or momelotinib, that could provide other new drugs for MPN patients.[20,21] Although ruxolitinib is a potent agent to treat splenomegaly and symptoms, some characteristics of other JAK-inhibitors found in early phase studies could be of particular interest in subsets of patients that currently do not benefit from ruxolitinib therapy; e.g. pacritinib did not worsen thrombocytopenia in patients with MF and low platelet counts.[22] On the other hand, momelotinib was found to induce interesting responses on anemia, specially in transfusion-dependent MF patients.[23] If these findings are confirmed in the ongoing phase III studies, along with a significant efficacy on splenomegaly and symptoms, they could help increase the armamentarium to treat MF patients and address specific therapeutic needs according to the main clinical need.

All these changes in the management of MPNs will clearly change the economic impact of these not so rare diseases. Diagnostic and prognostic work up costs will necessarily increase if a bone marrow biopsy is mandatory to diagnose all the three MPN subtypes as suggested in a recent proposal for up-dating the WHO diagnostic criteria.[24] To date, this biopsy is not routinely done in many centers to make a diagnosis of PV for example. In terms of prognosis, current classification of ET and PV patients relies on very simple markers: age and history of vascular events.[1] If one considers that assessment for mutations associated with a poor outcome is necessary for the proper management of younger patients, the cost of NGS techniques will further increase the cost of MPN base-line assessment. Finally, the cost of therapies is also increasing rapidly when considering the development of alternatives to HU, including IFNa and JAK inhibitors. Therefore, a real benefit for patients should be clearly evidenced for supporting

these new therapies. IFNa is currently being tested head-to-head against HU in different clinical studies in PV and ET patients, and this will hopefully soon provide clear evidence of its exact role in the management of these diseases (*clinicaltrials.gov identifiers: 01259856 and 01949805*). Ruxolitinib, the only approved JAK inhibitor to date in MPNs, provided clear benefit for many MF patients compared to other available therapies, as demonstrated in the COMFORT-2 study.[17] The recent RESPONSE study also showed its efficacy as second-line therapy after HU in PV,[19] a setting in which other drugs, usually much less expensive, can be used. Further studies in PV are needed to clarify the benefit of ruxolitinib in altering the natural history of PV in reducing risks of thrombosis and transformation. The burden of MPN therapy may, therefore, clearly and significantly increase in the coming years, and national and international societies will certainly have to propose evidence-based, fair and balanced guidelines for the management of MPNs and these will increasingly be based upon a personalized approach.[25]

Financial and other disclosures provided by the author using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are available with the full text of this paper at www.haematologica.org.

References

1. Barbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol. 2011;29(6):761-770.
2. Harrison CN, Campbell PJ, Buck G, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. N Engl J Med. 2005;353(1):33-45.
3. Campbell PJ, Scott LM, Buck G, et al. Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. Lancet. 2005;366(9501):1945-1953.
4. Mahon FX, Etienne G. Deep molecular response in chronic myeloid leukemia: the new goal of therapy? Clin Cancer Res. 2014;20(2):310-322.
5. Baccarani M, Castagnetti F, Gugliotta G, Rosti G. A review of the European LeukemiaNet recommendations for the management of CML. Ann Hematol. 2015;94(Suppl 2):141-147.
6. Kiladjian JJ, Cassinat B, Chevret S, et al. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. Blood. 2008;112(8):3065-3072.
7. Kiladjian JJ, Massé A, Cassinat B, et al. Clonal analysis of erythroid progenitors suggests that pegylated interferon alpha-2a treatment targets JAK2V617F clones without affecting TET2 mutant cells. Leukemia. 2010;24(8):1519-1523.
8. Lundberg P, Karow A, Nienhold R, et al. Clonal evolution and clinical correlates of somatic mutations in myeloproliferative neoplasms. Blood. 2014;123(14):2220-2228.
9. Guglielmelli P, Lasho TL, Rotunno G, et al. The number of prognostically detrimental mutations and prognosis in primary myelofibrosis: an international study of 797 patients. Leukemia. 2014;28(9):1804-1810.
10. Tenedini E, Bernardis I, Artusi V, et al. Targeted cancer exome sequencing reveals recurrent mutations in myeloproliferative neoplasms. Leukemia. 2014;28(5):1052-1059.
11. Dameshek W. Some speculations on the myeloproliferative syndromes. Blood. 1951;6(4):372-5.
12. Kiladjian JJ. The spectrum of JAK2-positive myeloproliferative neoplasms. Hematology Am Soc Hematol Educ Program. 2012;2012:561-566.
13. Harrison C. Rethinking disease definitions and therapeutic strategies in essential thrombocythemia and polycythemia vera. Hematology Am Soc Hematol Educ Program. 2010;2010:129-134.
14. Maxson JE, Gotlib J, Pollyea DA, et al. Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML. N Engl J Med. 2013;368(19):1781-190.
15. Gotlib J. World Health Organization-defined eosinophilic disorders: 2014 update on diagnosis, risk stratification, and management. Am J Hematol. 2014;89(3):325-337.
16. Gisslinger H, Gotic M, Holowiecki J, et al. Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET Study, a randomized controlled trial. Blood. 2013;121(10):1720-1728.
17. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. 2012;366(9):787-798.
18. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012;366(9):799-807.
19. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med. 2015;372(5):426-435.
20. Geyer HL, Mesa RA. Therapy for myeloproliferative neoplasms: when, which agent, and how? Blood. 2014;124(24):3529-3537.
21. Abdelrahman RA, Begna KH, Al-Kali A, Hogan WJ, Litzow MR, Tefferi A. Revised assessment of response and long-term discontinuation rates among 111 patients with myelofibrosis treated with momelotinib or ruxolitinib. Leukemia. 2015;29(2):498-500.
22. Komrokji RS, Seymour JF, Roberts AW, et al. Results of a phase 2 study of pacritinib (SB1518), a JAK2/JAK2(V617F) inhibitor, in patients with myelofibrosis. Blood. 2015;125(17):2649-2655.
23. Pardanani A, Abdelrahman RA, Finke C, et al. Genetic determinants of response and survival in momelotinib-treated patients with myelofibrosis. Leukemia. 2015;29(3):741-744.
24. Tefferi A, Thiele J, Vannucchi AM, Barbui T. An overview on CALR and CSF3R mutations and a proposal for revision of WHO diagnostic criteria for myeloproliferative neoplasms. Leukemia. 2014;28(7):1407-1413.
25. Harrison CN, Butt N, Campbell P, et al. Modification of British Committee for Standards in Haematology diagnostic criteria for essential thrombocythaemia. Br J Haematol. 2014;167(3):421-423.