Children and Adolescents with Chronic Myeloproliferative Neoplasms: Still an Unmet Biological and Clinical Need?

Tariq I. Mughal1, Michael W. Deininger2, Nicole Kucine3, Giuseppe Saglio4, Richard A. Van Etten5

Correspondence: Tariq I. Mughal (e-mail: tmughal911@hotmail.com).

The remarkable story of the classic chronic myeloproliferative neoplasms (MPN), a group of clonal hematological malignancies characterized by excessive accumulation of one or more myeloid cell lineages and an inherent ability to transform to acute leukemia, and views on its molecular genetics, biology and treatment continue to evolve.1,2 These neoplasms comprise of chronic myeloid leukemia (CML), defined by the presence of BCR-ABL1, and the BCR-ABL1-negative disorders, polycythemia vera (PV), essential thrombocytopenia (ET) and primary myelofibrosis (PMF). The term myelofibrosis (MF) includes primary myelofibrosis (PMF) and post-PV and post-ET MF. Though the diagnostic criteria and classification in accordance to the revised 2016 WHO MPN criteria are often utilized in adults, adolescents and children, there are emerging data pointing to genetic differences which impact phenotypic characteristics, treatment and prognosis.3,4 In addition, most of the current risk scores used for adults have not been validated in children and adolescents, with the sole exception of the EUTOS long term survival score (ELTS) that may be used to predict progression-free survival, but not overall survival (OS).5,6

Epidemiology and genetics

With the sole exception of juvenile myelomonocytic leukemia (JMMML) and possibly cutaneous mastocytosis, the incidence of all MPNs increases with age.8 This observation lends support to the potential link between aging and inflammation (‘inflammaging’) as a driver of clonal evolution and selection in MPNs.9 MPNs are extremely rare in children and adolescents, and even rarer in infants. Also, unlike in adult MPNs, clonal hematopoiesis of indeterminate potential (CHIP) is unlikely in pediatric populations, and hence unlikely to play a role in the pathogenesis of pediatric MPNs.10,11 That said, there is some evidence suggestive of the notion of colonization of hematopoietic tissues by intestinal microbe being associated with the development of MPN in TET2 deficient mice, a process mediated by IL-6 and linking progression from CHIP to MPN to extrinsic ‘macro-environmental’ factors.12-14 Such observations lend some support to the hypothesis supporting the risk of a history of infection or autoimmune disease and myeloid malignancies.15

Children and adolescents with CML do not appear to have cytogenetic abnormalities in addition to the Philadelphia chromosome, but some have been observed to harbor different BCR-ABL1 breakpoint distribution and additional somatic mutations, often resembling those seen in BCR-ABL1-positive acute lymphoblastic leukemia (ALL).16,17 The leukemogenesis of pediatric BCR-ABL1-negative MPNs is associated with genetic drivers that are similar to those in adults, but with important differences. For example, a lower frequency of mutations in all 3 founding driver genes, JAK2, MPL and CALR, and an absence of mutations in any of the about 100 known MPN-associated genes have been reported in a significant proportion of children and adolescents diagnosed with MPNs.18-22 It is of interest that many children without these mutations have a diagnosis of hereditary thrombocytopathy or ET. Some of these children were reported to harbor MPL S105A, which is actually MPL S105N, and in keeping with the original report in 2007,21,22. The precise significance and role of co-existing germline, driver and secondary somatic mutations in relation to age at the onset of the MPN clone are also poorly understood.23 Younger patients appear to develop PV...
following the acquisition of a single somatic JAK2V617F mutation, in contrast to older patients in whom this mutation is often accompanied by secondary mutations.24 Interestingly, a diagnosis of MPN has been made in several children who were previously observed to have JAK2V617F mutations detected in the newborn screening cards. Indeed, data from the Swedish-familial cancer registry suggest a genetic predisposition to acquiring MPN driver mutations at younger ages in patients with a high-risk family history. It is likely that inherited and environmental factors are shared in this genetic predisposition.25 Indeed, anecdotal reports of a TERT single-nucleotide variant has also been reported, especially in females, and associated with exposure to benzene and toluene.26

The International Pediatric Registry data suggest the incidence of CML in children and adolescents to be considerably lower than that in adults, with an annual incidence of about 0.7 per 1,000,000 and 1.2 per 1,000,000, respectively.27 The incidence of PV and ET has been estimated to be about 1 to 2 cases per 10,000,000 children and adolescents annually; the incidence of PMF and MF is unknown and considered extremely low.28 There are also some reports suggesting that with increased pediatric-MPN awareness, incidence rates could rise.

Clinical and treatment issues in pediatric MPNs

Clinically, children and adolescents with CML in chronic phase often present with proliferative features, such as splenomegaly and higher leucocyte counts, compared with adults. Additionally, a greater proportion of them have advanced disease at diagnosis.29 Pediatric BCR-ABL1-negative MPN patients can present with thrombotic events, in particular when associated with JAK2 mutations.30–32 The risk of all thrombosis is quite low overall, estimated at about 9% for PV and 4% for ET. In contrast, the incidence of venous thrombotic events appears to be quite high – estimated at about 85% in the London series, whilst hemorrhagic complications are rare (<5%).33 Children with PV and ET also tend to exhibit higher white blood counts and often present with hepatosplenomegaly.32

For adult patients with CML, the licensed ABL1-tyrosine kinase inhibitors (TKI), accord an OS not dissimilar from that of the general population, and about one-half of patients achieving sustained deep molecular remission (DMR) are able to maintain DMR following TKI discontinuation. Regardless, further prospective and larger studies assessing discontinuing TKIs successfully are urgently required in children and adolescents with CML prior to the introduction of TFR into the pediatric clinics outside of clinical trials.

The recent approval of nilotinib and dasatinib for pediatric patients has also complicated the decision-making process regarding allogeneic stem transplantation (allo-SCT). Clearly, patients who have a suboptimal response or failure to 2 lines of TKIs should be considered for an allo-SCT. Allo-SCT should also be offered to CML patients who acquire the T315I mutation in BCR-ABL1, since the third generation TKI, ponatinib, is not currently licensed for children and adolescents. A recent comprehensive survey of 247 US-based pediatric hematologists’ attitude towards an optimal treatment algorithm suggest that most do not support the use of allo-SCT for first-line therapy, and about 40% support it if suitable donor was available.35 However, the vast majority support the use of allo-SCT following 2 lines of TKI therapy.

For adult patients with MF a qualified therapeutic success with a substantial relief of disease-related symptoms, splenomegaly and survival benefit has been observed with the only licensed JAK12 inhibitor, ruxolitinib,36,37 but therapy-related anemia is often an anticipated downside.38 Allo-SCT, however, remains the only treatment which can achieve long term remission and potential cure, but is associated with considerable morbidity and mortality.39 There are, however, scanty data with regards to the use of JAK inhibitors and allo-SCT in children and adolescents. Indeed, at present, there is no firm consensus on the optimal clinical management of children with PV, ET, or MF. Hydroxyurea is used frequently, but long-term safety remains unclear, and there is limited data available on use of interferon alpha in this patient population.30,32

Future prospects

Arguably, despite much progress in the field of MPNs, and in particular CML, many important issues pertaining to the diagnosis, classification, risk stratification and treatment of children and adolescents remain. Mutational profiling has revealed important differences between adult and pediatric MPNs which influence the biology and prognosis, but larger contemporary cohorts with long-term follow-up are needed to assess this and the impact on treatment appropriately. In this
regard, it is of note that during this year’s International Childhood Cancer Awareness Day, both the Society for Pediatric Oncology Europe (SIOPE) and Childhood Cancer International (CCI) on Pediatric Hematology and Oncology launched a manifesto calling for the European Parliament to maintain and reinforce support. The rarity of pediatric MPNs and the increasing recognition of long-term side-effects of successful treatments, including cardiovascular, endocrine, growth and psychological issues underscores the urgent need for agreeable funding and collaborations worldwide.

Acknowledgments

The authors thank the participants and faculty of the thirteenth Post-ASH CML-MPN workshop, Dr Alpa Parmar for her organizational skills, and Incyte Corporation, Novartis Oncology, Pharma Essentia and Alpine Oncology Foundation for unrestricted grant support.

References

1. Mughal TI, Radich JP, Deininger MW, et al. Chronic Myeloid Leukemia: Reminiscences and dreams. Haematologica. 2016;101:541–558.
2. Deininger MWN, Tyner JW, Solary E. Turning the tide in myelodysplastic/myeloproliferative neoplasms. Nat Rev Cancer. 2017;17:425–440.
3. Arber DA, Orazi A, Passamonti F, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127:2391–2405.
4. Wong WJ, Hasseriyan R, Pinkus GS, et al. JAK2, CALR, MPL and ASXL1 mutational status correlates with distinct histological features in philadelphia chromosome-negative myeloproliferative neoplasms. Haematologica. 2018;103:663–668.
5. Hijiya N, Suttorp M. How I treat chronic myeloid leukemia in children and adolescents blood. 2019;pre-published; doi: 10.1182/ blood.201888233.
6. Gurea-Salas D, Glauche I, Tauer JT, et al. Can prognostic scoring systems for chronic myeloid leukemia as established in adults be applied to pediatric patients? Ann Hematol. 2015;94:1363–1371.
7. Mughal TI, Perrmaraju N, Radich JP, et al. Emerging translational science discoveries, clonal approaches and treatment trends in chronic myeloproliferative neoplasms. Hematol Oncol. 2019;1:1–13. doi: 10.1002/hon.2622.
8. Srour SA, Devesa SS, Morton LM, et al. Incidence and patient survival of myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms in the United States, 2001–12. Br J Haematol. 2016;174:382–396.
9. Fulop T, Wilkowksi JM, Olivieri F, et al. The integration of inflamming in age-related diseases. Semin Immunol. 2018;40:17–35.
10. Elias HK, Bryder D, Park CY. Molecular mechanisms underlying lineage bias in aging hematopoiesis. Semin Hematol. 2017;54:4–11.
11. Chambers SM, Shaw CA, Gatza C, et al. Aging hematopoietic stem cells decline in function and exhibit epigenetic dysregulation. PLoS Biol. 2007;5:e201.
12. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371:2488–2498.
13. Fleischman AG, Aichberger KJ, Luty SB, et al. TNF alpha facilitates clonal expansion of JAK2V617F positive cells in myeloproliferative neoplasms. Blood. 2011;118:6392–6398.
14. Meisel M, Hinterleitner R, Pacis A, et al. Microbial signals drive pre-leukemic myeloproliferation in a T-cell-deficient host. Nature. 2018;557:580–584.
15. Kristinsson SY, Bjorkholm M, Hultcrantz M, et al. Chronic immune stimulation might act as a trigger for the development of acute myeloid leukemia or myelodysplastic syndromes. J Clin Oncol. 2011;29:2897–2903.
16. Hijiya N, Schultz KR, Metzler M, et al. Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. Blood. 2016;127:392–399.
17. Krumholz M, Karl M, Tauer JT, et al. Genomic BCR-ABL1 breakpoints in pediatric chronic myeloid leukemia. Genes Chromosomes Cancer. 2012;51:1045–1053.
18. Karow A, Niemold R, Lundberg P, et al. Mutational profile of childhood myeloproliferative neoplasms. Leukemia. 2015;29:2407–2409.
19. Ernst T, Busch M, Rinke J, et al. Frequent ASXL1 mutations in children and young adults with chronic myeloid leukemia. Leukemia. 2018;32:2046–2049.
20. Kucine N, Viny AD, Rampal R, et al. Genetic analysis of five children with essential thrombocythemia identified mutations in cancer-associated genes with roles in transcriptional regulation. Haematologica. 2016;101:e237–e239.
21. Defour J-P, Levy G, Leroy E, et al. The S505A thrombopoietin receptor mutation in childhood hereditary thrombocythemia and essential thrombocythemia is S505N: single letter amino acid code matters. Leukemia. 2019;33:563–564.
22. Teofilii L, Giona F, Martini M, et al. Markers of myeloproliferative diseases in childhood polycythemia vera and essential thrombocythemia. J Clin Oncol. 2007;25:1048–1053.
23. Kelly K, McMahon C, Langabeer S, et al. Congenital JAK2V617F polycythemia vera: where does the genotype-phenotype diversity end? Blood. 2008;112:4356–4357.
24. Fowles JS, How J, Allen MJ, et al. Young versus old age at diagnosis confers distinct genomic profiles in patients with polycythemia vera. Leukemia. 2019;Pre-pub April 2019; doi.org/10.1038/s41375-018-0349-9.
25. Sud A, Chattopadhyay S, Thomsen H, et al. Familial risk of acute myeloid leukemia, myelodysplastic syndromes, and myeloproliferative neoplasms. Blood. 2018;132:973–976.
26. Triffa AP, Bănescu C, Tevet M, et al. TERT rs2736100 A>C SNP and JAK2 46/1 haplotype significantly contribute to the occurrence of JAK2 V617F and CALR mutated myeloproliferative neoplasms – a multicentric study on 529 patients. Brit J Haem. 2016;174:219–226.
27. Gunes AM, Millot F, Kalwak K, et al. Features and Outcome of Chronic Myeloid Leukemia (CML) at Very Young Age: Data from the International Pediatric CML Registry (i-CML-Ped Study). Blood. 2018;132:1748.
28. Hofmann I. Myeloproliferative neoplasms in children. J Hematop. 2015;8:143–157.
29. Millot F, Guilhot J, Suttorp M, et al. Advanced phases at diagnosis of childhood chronic myeloid leukemia: the experience of the international registry for chronic myeloid leukemia (CML) in children and adolescents (i-CML-Ped Study). Blood. 2017;130:316.
30. Barbui T. How to manage children and young adults with myeloproliferative neoplasms. Leukemia. 2012;26:1452–1457.
31. Kucine N, Al-Kawaz M, Haje D, et al. Difficulty distinguishing essential thrombocythaemia from polycythaemia vera in children with JAK2V617F-positive myeloproliferative neoplasms. Br J Haematol. 2019;185:136–139.
32. Ianotto JC, Curto-Garcia N, Lauermannova M, et al. Characteristics and outcomes of patients with essential thrombocythemia or polycythemia vera diagnosed before 20 years of age, a systematic review. Haematologica. 2019;epub ahead of print, doi: 10.3324/haematol.2018.200832.
33. Brujin CMA, Millot F, Suttorp M, et al. Discontinuation of imatinib in children with chronic myeloid leukaemia in sustained deep molecular remission: results of the STOP IMAPED study. Br J Haematol. 2019;185:718–724.
34. Sauselle B, Richter J, Guilhot J, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukemia (EURO-SKII): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. Lancet Oncol. 2018;19:747–757.
35. Anolina JR, Burke MJ, Hijiya N, et al. Practice patterns of physician treatment for pediatric chronic myelogenous leukemia. Biol Blood Marrow Transplant. 2019;25:321–327.
36. Verstovsek S, Mesa RA, Gotti J, et al. Long-term treatment with ruxolitinib for patients with myelofibrosis: 5-year update from the randomized, double-blind, placebo-controlled, phase 3 COMFORT-I trial. J Hematol Oncol. 2017;10:55.
37. Harrison CN, Vannucchi AM, Kiladjian JJ, et al. Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis. Leukemia. 2016;30:1701–1707.
38. Nayarmon L, Mascarénhas J. Myelofibrosis-related anaemia: current and emerging therapeutic strategies. HemaSphere. 2017;1:e1.
39. Passamonti F. Stem cell transplant in MF: it’s time to personalize. Blood. 2019;133:2118–2120.