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Chronic Myeloproliferative Neoplasms: Some Remaining Challenges

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Following millennia of clinical medicine's efforts to embrace personalized, more effective and kinder treatments, arguably, it is the lessons garnered from patients with chronic myeloid leukemia (CML) in the chronic phase (CP) that appear to be moving us closer to the prospect of precision cancer medicine.[1] The *BCR-ABL1* fusion gene encodes the oncoprotein BCR-ABL1 with a constitutive active tyrosine kinase activity that is the sole primary driver of the CP of CML. The discovery in 1996 that this kinase activity could be inhibited by imatinib mesylate (imatinib), a first-generation tyrosine kinase inhibitor (TKI) was pivotal. It established a new paradigm of targeted treatment for diverse cancers, in which relatively nonspecific and often toxic drugs are gradually being replaced by a cornucopia of safer, and in some cases, better targeted therapies and immunotherapies.[2]

Imatinib substantially and durably reduces the number of CML cells in the CP at a daily oral dose of 400 mg, and the life expectancy of most patients now approaches that of the general population.[3] The greatest advance is in those patients who achieve a complete cytogenetic response within 2 years of starting imatinib leading to life spans indistinguishable from the general population.[4] These impressive results with imatinib therapy have had profound effects on the natural history of CML and its prevalence. Current estimates suggest that in the United States, where about 5500 new cases are diagnosed annually, the prevalence may well increase to about 120,000 by 2020 and to about 200,000 by 2050.[5] However, imatinib is far from perfect, with only approximately 60% of patients remaining on the standard daily dose of 400 mg after 6 years due to either lack of drug tolerance or drug resistance. Imatinib induces responses also in the more advanced phases of CML, but these responses are not durable. The 3 newer second-generation TKIs, dasatinib, nilotinib, and bosutinib, and the third-generation TKI, ponatinib, are all more potent than imatinib in in vitro assays. Current clinical experience suggests that patients treated with these newer TKIs achieve deeper and faster molecular responses than with standard-dose imatinib, but the precise benefits of such superior responses remain an enigma.[6]

Thus far, there is little evidence of a statistically significant improvement in overall survival with second-generation TKIs, though long-term follow-up confirmed a superior rate of freedom from progression compared with patients with less deep molecular responses at the same time points.[7] It is possible, though not confirmed widely, that many of these patients will be able to discontinue therapy safely (treatment-free remission [TFR]) and effectively once they have been in a complete molecular remission (CMR) for about 24 months.[8] Indeed, several studies, such as STIM, Euro-SKI, Australian CML-study, TWISTER, and other smaller studies, support the TFR concept.[9,10] Furthermore, the European Medicines Agency (EMA) recognized the significance of TFR, not just in terms of physical and financial toxicity for patients, but also for the society at large. It is possible, but no confirmed that the second- and third-generation TKI accord a greater potential in achieving TFR, and this remains the subject of ongoing studies. Recent expert statements provide a framework for consensus development, which should define the minimum acceptable *BCR-ABL1* transcript levels for TFR, precise definition of sustained CMR, and the impact of coexisting comorbidities, among others.[11,12]

Randomized prospective studies have documented the occurrence of serious TKI-related cardiovascular events in CML patients with and without pre-existing cardiac conditions or risk factors, including adverse metabolic changes, diabetes mellitus, and lipid profile changes.[13–17] Furthermore, meta-analyses and population-based studies clarify such risks as class effects or specific to certain TKIs.[18–20] Clearly in efforts to effectively manage comorbidities and minimize treatment-related adverse events, in particular when commencing or switching to TKIs known to carry the highest risk for cardiovascular toxicity, robust recommendations for baseline and subsequent interval testing of indicators of vascular disease need to be in place. Additional tools, such as the Framingham risk model and the European Society of Cardiology-Score, and novel treatment approaches to suppress multiresistant CML subclones, such as "TKI rotation therapy," are being tested.[21–23] Other areas of

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clinical importance include prediction of resistance to TKIs by assessing *BCR-ABL1* mutant subclone expansion, particularly in those who display 2 or more mutations in the *BCR-ABL1* kinase domain.[24] The best treatment approaches for pediatric patients remain unclear. Recent work has confirmed the use of dasatinib as an effective treatment, with a safety profile similar to that seen in adults, though, interestingly, no examples of pleural or pericardial effusions or pulmonary arterial hypertension were noted.[25]

For patients with *BCR-ABL1*-negative myeloproliferative neoplasms (MPNs), clearly there was significant enthusiasm following the discovery of a gain-of-function mutation of JAK2 in 2005.[26] Much has been learned about the genomic landscape and recent work, such as the importance of the order of acquisition of the mutations and their impact on the phenotype and clinical characteristics, including risks of thrombosis and prognosis, has now been garnered.[27,28] Recent revisions to the World Health Organization (WHO) classification and diagnostic criterion for all subtypes of MPNs, concomitantly with the introduction of genomic prognostic scoring systems, genetically inspired prognostic scoring system and mutation-enhanced international prognostic scoring systems for transplant-age patients (MIPSS70 and MIPSS70-plus) for patients with primary myelofibrosis (PMF), are noteworthy and impact clinical care.[29–32] Though specific for patients with PMF, in the real world, these prognostic scoring systems are being used for all patients with myelofibrosis (MF), which include PMF, postpolycythemia vera MF (Post-PV-MF), and postessential thrombocythemia MF (Post-ET-MF).

Ruxolitinib, a JAK1 and a type 1 JAK2 inhibitor with a short half-life, was licensed by the Food and Drug Administration in 2011 for patients with intermediate (with no specification for intermediate-1 or -2) and high-grade MF, and by the EMA in 2013 for patients with significant constitutional symptoms and splenomegaly, based on randomized trials.[33,34] Ruxolitinib does not appear to exert significant disease-modifying effects, with a minor effect on bone marrow fibrosis and $JAK2^{V617F}$ allelic burden.[35,36] The ReTHINK trial attempted to assess the precise role of the drug in patients with high-risk MF without significant splenomegaly or symptoms, but had to be closed because of poor accrual.[37] Another area of concern is the resistance to ruxolitinib, the mechanism of which remains poorly understood.

The European LeukemiaNet (ELN) recently updated their treatment recommendations for all Philadelphia chromosome-negative MPNs,[38] and included the WHO revisions, the newer prognostic scoring systems, and also the results of the randomized MAJIC trial.[39,40] The MAJIC trial is noteworthy of observing the lack of superiority of ruxolitinib compared to current second-line therapies for patients with ET. Ruxolitinib demonstrated some clinical efficacy in ET, but was only superior in terms of symptom control.[40] The ELN expert consensus clinical management statements include the importance of health-related quality-of-life and the controversial iron-supplementation needs for some cases with PV following frequent phlebotomy. It also discusses the updates on hydroxyurea-resistant or -intolerant patients with PV and the benefit from the use of long-acting interferon alpha or ruxolitinib. Indeed, the current results of ropeginterferon alpha 2b versus hydroxyurea as frontline therapy for patients with PV demonstrate more complete hematologic and molecular responses following interferon treatment, compared with hydroxyurea after 2 years.[41]

The clinical development of next-generation JAK2 inhibitors has been difficult with many studies being discontinued due to the emergence of serious neurotoxicity, in particular Wernicke's encephalopathy.[42] Fedratinib's development in MF was discontinued in 2013, and is now being re-evaluated.[43] It was previously shown to be superior to placebo for control of splenomegaly and symptoms in patients with MF in the Jakarta I study, in addition to be active in the second-line setting for patients with MF who had previously been on ruxolitinib in the Jakarta II study.[43,44] Another JAK2 inhibitor, pacritinib, previously shown to be active in the PERSIST-1 and PERSIST-2 studies, is undergoing further development with refinement of optimal dosage.[45,46] And the recent phase 3 study results show pacritinib 200 mg twice daily to be significantly better than best available therapy, including ruxolitinib, for reducing splenomegaly and clinical symptoms in patients with MF and thrombocytopenia, for both previously untreated and those who had received prior ruxolitinib. Momelotinib, a JAK2 inhibitor, was tested in the SIMPLIFY-1 study in late 2017, but the trial failed to meet its primary endpoint.[47,48] In addition to JAK inhibition and interferons, many other investigational agents, either alone or in combination with ruxolitinib, are being tested. These include hedgehog, aurora kinase, SMAC, HDAC, and MDM2 inhibitors, in addition to the JAK2-allosteric inhibitors, such as LS104 and ON044580, which have a greater specificity for $JAK2^{V617F}$ and are inhibitory in a non-ATP-competitive manner, and were recently reviewed.[24]

The success of targeted therapy for patients with CML in CP has been contingent upon *BCR-ABL1* being the founder lesion in every cell, and minimal genetic diversity. Resistance can be an issue, but many patients can achieve durable second and subsequent remissions, following a switch to an alternative TKI or an allogeneic stem cell transplant. By contrast, clinical progress in other subtypes of MPNs, which can demonstrate significant genetic diversity, has been qualified and limited to few patients. Interferons and ruxolitinib are useful in some patients with MF and PV.

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