Anticipate Your Next Move in Chronic Myeloid Leukaemia Patient Management

This symposium took place on the 13th June 2019, as part of the 24th European Hematology Association (EHA) Congress in Amsterdam, the Netherlands

Chairpeople: Jeroen Janssen[1]

Speakers: Jeroen Janssen,[1] Jane Apperley,[2] Simona Soverini,[3] Hugues de Lavallade[4]

1. Amsterdam UMC, Amsterdam, the Netherlands
2. Imperial College London, London, UK
3. University of Bologna, Bologna, Italy
4. King's College London, London, UK

Disclosure: Dr Janssen has received research funding from BMS and Novartis; received honoraria from Incyte, Novartis, and Pfizer; and is the founder of HematologyApp, supported by BMS, Daiichi-Sankyo, Incyte, Janssen, MSD, Pfizer, Roche, and Takeda. Prof Apperley has received honoraria and research funding from Ariad, Incyte, Novartis, and Pfizer; and honoraria from BMS. Prof Soverini has provided consultancy for BMS, Incyte, and Novartis. Dr de Lavallade has received honoraria from BMS, Incyte, Novartis, and Pfizer; and has received research grants from ARIAD/Incyte and BMS.

Acknowledgements: Medical writing assistance was provided by Tom Feys, Ariez International, Bruges, Belgium.

Support: The symposium and the writing and publication of the article was funded by Incyte. The views and opinions expressed are those of the speakers and not necessarily of Incyte.

Citation: EMJ. 2019;4[4]:33-36.

Meeting Summary

Treatment decisions in chronic myeloid leukaemia (CML) are complex and require the evaluation of many factors at each stage of therapy. Many patients will become resistant or intolerant to the first and subsequent lines of tyrosine kinase inhibitors (TKI) they receive, requiring them to switch to a different TKI. Clinicians are faced with many considerations when choosing subsequent treatments and an important issue is how best to manage failure on a second-generation TKI. During an interactive and case-based, Incyte-sponsored, satellite symposium at the 2019 European Hematology Association (EHA) congress, Dr Janssen and Prof Apperley discussed the current best practices for managing patients failing imatinib or second-generation TKI, considering whether second-generation TKI should be used sequentially and the timing of the introduction of a third-generation TKI (ponatinib). Dr Soverini and Dr de Lavallade discussed how regular *BCR-ABL* response monitoring and mutational analysis are integral to CML patient management. They highlighted the clinical relevance of low-level mutations and the necessity to prevent clonal expansion of these TKI-resistant mutants, and the accumulation of additional mutations, by switching to an effective TKI in a timely manner.

Introduction

The significant advances in the treatment of patients with CML over the last two decades have resulted in an improved prognosis for most patients, contributing to their life expectancy approaching that of the general population.[1] Improvements in the prognosis of CML patients was also accompanied by a shift in the management of the disease and the treatment objectives. While in 2001 the treatment objective was to prolong the survival of patients, the main treatment goal today is for patients to achieve a deep molecular response, which gives them the best chance to successfully stop treatment. The introduction of imatinib revolutionised the treatment landscape of CML, and with this agent the majority of patients will eventually attain a deep molecular response;[2,3] however, for a proportion of patients the treatment outcomes with imatinib are unsatisfactory. Imatinib and second-generation TKI can become inactive once point mutations in the *BCR-ABL* TKI binding domain appear.[4] When this occurs, there is a need for an alternative TKI that is active in the presence of such resistant mutations. During an interactive and case-based satellite symposium, hosted by Incyte during the 2019 EHA meeting, Dr Janssen and Prof Apperley discussed the current best practices in CML patients failing on imatinib or a second-generation TKI, after which Dr Soverini and Dr de Lavallade discussed the technical aspects related to mutation testing in CML.

Dealing with Imatinib or Second-Generation Tyrosine Kinase Inhibitor Failure in Chronic Myeloid Leukaemia

Doctor Jeroen Janssen

Over the last decade, regular *BCR-ABL* response monitoring has become an important part of managing CML patients who are treated with a TKI. This approach allows physicians to quickly identify patients with a suboptimal response ('warning' or 'failure'), as defined by the European Leukemia Network (ELN) criteria, and switch them to an alternative TKI. In the case of a 'warning', the outcome might improve, but close follow-up is warranted. In the case of 'failure', immediate action is required (i.e., a TKI switch).[5] In the case of a 'warning' or 'failure', the ELN and National Comprehensive Cancer Network (NCCN) guidelines on CML recommend a mutational analysis of the *BCR-ABL* kinase domain.[5-7] If a mutation is discovered, it is important to choose the appropriate next TKI, e.g., by using the traffic-light coded heat map that lists the sensitivity of most common mutations for all currently available TKI.[8]

What can we Expect from Switching Between Second-Generation Tyrosine Kinase Inhibitors?

Professor Jane Apperley

There is a lack of clinical data on the effect of switching from one second-generation TKI to another (i.e., switching between nilotinib, dasatinib, or bosutinib) after initial failure on imatinib. The scarce data available indicate that the rate of complete cytogenetic responses to a second-generation TKI in the third-line setting was low (ranging from 11% to 32%).[9-11] Furthermore, the durability of these responses was limited;[10-12] for example, in a Phase I/II study 71% of the patients who received bosutinib after imatinib and dasatinib/nilotinib failure discontinued therapy within 2 years.[12] Notably, almost half of the patients in these trials switched between second-generation TKI for reasons of intolerance, and the proportion of truly resistant patients was low. As such, these studies do not provide firm support for a switch between second-generation TKI in TKI-resistant patients.[9-12]

When switching from a second to a third-generation TKI (i.e., ponatinib), deep and durable responses can be achieved. In the PACE trial, chronic-phase CML patients treated with ponatinib after resistance or intolerance to dasatinib or nilotinib resulted in a 49% complete cytogenetic response and a 35% major molecular response. An MR4.5 was achieved by 20% of patients (Figure 1).[13] Importantly, the response to ponatinib proved to be durable with 59% of the responders remaining in major molecular response after 5 years. The latter translated into an estimated overall survival of 73% at 5

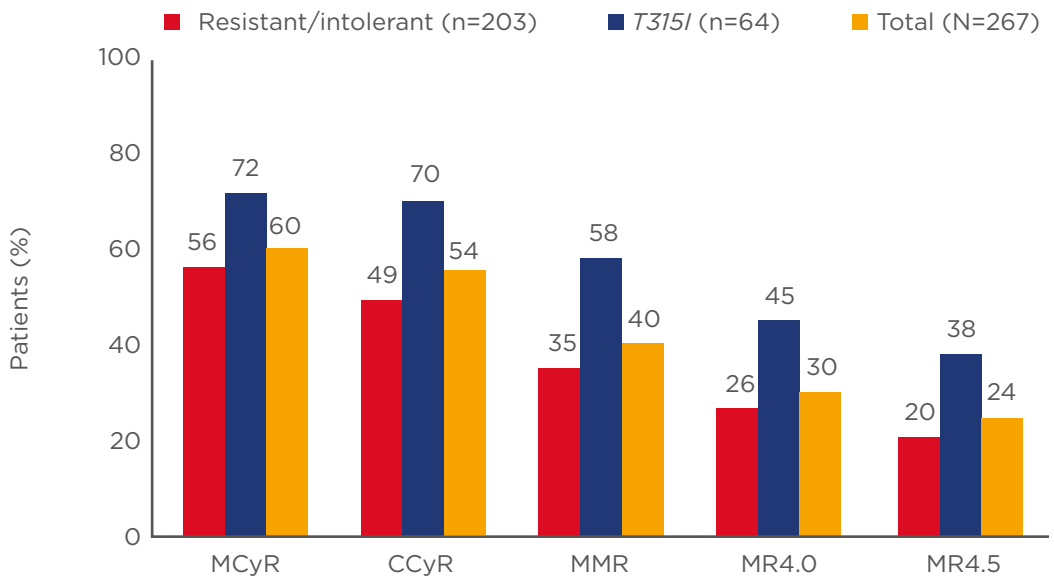

Figure 1: Rates of responses to ponatinib in the PACE trial in patients with chronic-phase chronic myeloid leukaemia.

CCyR: complete cytogenetic response; MCyR: minor cytogenetic response; MMR: major molecular response; MR4.0/4.5: deep molecular response 4.0/4.5.

Adapted from Cortes et al.[13]

years.[13] For patients treated with ponatinib, close monitoring and the use of preventive measures are warranted to decrease the risk of toxicity.[14] Finally, for the small proportion of patients who are not responding to multiple lines of therapy, including ponatinib, a donor search for an allogeneic stem cell transplantation can be started.[14]

Optimising Mutation Testing in Chronic Myeloid Leukaemia

Doctor Simona Soverini and Doctor Hugues de Lavallade

As indicated before, patients with a suboptimal response or a TKI treatment failure should undergo mutational analysis, as recommended by the ELN and NCCN guidelines.[5-7] Sanger sequencing has long been the gold standard to perform this mutational analysis, but evidence has accumulated showing that next-generation sequencing (NGS) is markedly more sensitive. NGS can detect mutations with a sensitivity of approximately 3%, while Sanger sequencing has a sensitivity of 15–20%.[15,16] As such, NGS allows the detection of TKI-resistant mutations much earlier and at lower frequency levels. Data generated by Dr Soverini indicate that the detection of low-level mutations is of clinical relevance given the fact that all these low-level mutations expand if there is no switch to an appropriate TKI.[17,18] In addition, recent data reported by Schmitt et al.[19] indicate that advanced CML and Philadelphia chromosome-positive acute lymphoblastic leukaemia patients with *BCR-ABL* mutations have a greater likelihood of acquiring additional mutations. With this in mind, Dr Soverini and Dr de Lavallade concluded that it is essential to prevent the clonal expansion of these TKI-resistant mutants and the accumulation of additional mutations by switching to an appropriate TKI in a timely manner.

References

1. Bower H et al. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. J Clin Oncol. 2016;34(24):2851-7.
2. Hehlmann R et al. Deep molecular response is reached by the majority of patients treated with imatinib, predicts survival, and is achieved more quickly by optimized high-dose imatinib: Results from the randomized CML-study IV. J Clin Oncol. 2014;32(5):415-23.
3. Hochhaus A et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med. 2017;376(10):917-27.
4. Soverini S et al. Implications of *BCR-ABL1* kinase domain-mediated resistance in chronic myeloid leukemia. Leuk Res. 2014;38(1):10-20.
5. Baccarani M et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872-84.
6. Soverini S et al. *BCR-ABL* kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: Recommendations from an expert panel on behalf of European LeukemiaNet. Blood. 2011;118(5):1208-15.
7. Radich JP et al. Chronic myeloid leukemia, Version 1.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16(9):1108-35.
8. Redaelli S et al. Three novel patient-derived *BCR/ABL* mutants show different sensitivity to second and third generation tyrosine kinase inhibitors. Am J Hematol. 2012;87(11):E125-8.
9. Ibrahim AR et al. Efficacy of tyrosine kinase inhibitors (TKIs) as third-line therapy in patients with chronic myeloid leukemia in chronic phase who have failed 2 prior lines of TKI therapy. Blood. 2010;116(25):5497-500.
10. Garg RJ et al. The use of nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors: Long-term follow-up. Blood. 2009;114(20):4361-8.
11. Giles FJ et al. Nilotinib is active in chronic and accelerated phase chronic myeloid leukemia following failure of imatinib and dasatinib therapy. Leukemia. 2010;24(7):1299-301.
12. Khoury H et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood. 2012;119(15):3403-12.
13. Cortes JE et al. Ponatinib efficacy and safety in Philadelphia chromosome–positive leukemia: Final 5-year results of the Phase 2 PACE trial. Blood. 2018;132(4):393-404.
14. Müller MC et al. Ponatinib in chronic myeloid leukemia (CML): Consensus on patient treatment and management from a European expert panel. Crit Rev Oncol Hematol. 2017;120:52-9.
15. Baer CR et al. Prospective next-generation sequencing of mutations in the *ABL1* kinase domain in CML patients lacking optimal response according to ELN Guidelines. Blood. 2016;128(22):3100.
16. Rohlin A et al. Parallel sequencing used in detection of mosaic mutations: Comparison with four diagnostic DNA screening techniques. Hum Mutat. 2009;30(6):1012-20.
17. Soverini S et al. Clinical relevance of low burden *BCR-ABL1* mutations detectable by amplicon deep sequencing (DS) in Philadelphia-positive (Ph+) acute lymphoblastic leukemia (ALL) patients (pts): The type of mutation matters. Blood. 2015;126(23):2489.
18. Soverini S et al. Next generation sequencing for sensitive detection of *BCR-ABL1* mutations relevant to tyrosine kinase inhibitor choice in imatinib-resistant patients. Oncotarget. 2016;7(16):21982-90.
19. Schmitt MW et al. Single-molecule sequencing reveals patterns of preexisting drug resistance that suggest treatment strategies in Philadelphia-positive leukemias. Clin Cancer Res. 2018;24(21):5321-34.