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Editorial

Chronic Myeloid Leukemia - Chronic Phase: The START and STOP Challenges

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EDITORIAL

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the proliferation of the granulocytic cell line while maintaining its capacity to differentiate. It is caused by a cytogenetic aberration in more than 95 % of the cases: the Philadelphia chromosome that results from the reciprocal translocation between the long arms of the chromosomes 9 and 22 [t(9;22)]. CML presents in 3 clinical phases: the chronic phase, the accelerated phase and the blast crisis.

The goal of treatment is to reduce these leukemic cells harboring the translocation t(9;22). It has three-fold objectives: the complete hematologic remission defined as normal complete blood counts and physical exam, the cytogenetic remission defined as disappearance of the cells with the Philadelphia chromosome and the major molecular response (MMR). The MMR is defined as a quantitative polymerase chain reaction (PCR) of the chimeric BCR-ABL RNA level ≤0.1% on the International Scale (IS). It represents a potential for cure and an attempt towards increasing survival.

Imatinib remained the only available tyrosine kinase inhibitor (TKI) for CML for many years. However, in the last decades, the guidelines changed concerning the goal of treatment, as well as the first and second line therapies. According the National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO), European LeukemiaNet (ELN) guidelines, Imatinib mesylate is still approved in the first line treatment for chronic phase CML. Additionally, the second generation TKIs Dasatinib, Nilotinib and Bosutinib can also be used as a first line treatment. According to the following phase III trials done in treatment naïve CML patients, the DASISION trial (comparing the Imatinib to Dasatinib), the ENESTnd trial (comparing the Nilotinib to Imatinib) and the BFORE trial (comparing Imatinib to Bosutinib), there was no difference in the 5-years overall survival between the head to head compared TKIs. However, the second line tyrosine kinase inhibitors were able to induce higher rates of earlier complete cytogenetic responses (CCyR) and major molecular response compared with Imatinib. Furthermore, they were also associated with a deeper molecular response (MMR4,5) as well as lower rates of progression to accelerated phase and blast crisis. Despite the absence of a difference in the overall survival, the CCyR is a major determinant of CML outcome regardless of the MMR status. However, when we compare the Imatinib to the next generation agents, these latter are associated with a higher toxicity profile and increased costs, knowing that Imatinib is still highly effective. Thus, the choice of the TKI depends on the medical history and is based on risk stratification according to 2 scoring systems: the Sokal and Hasford scores. The patients with intermediate or high risk chronic phase - CML may get more benefit from second generation TKIs showing higher rates of MMR and lower risk of disease progression.

Besides, the recommendations used to be in favor of continuing the TKI therapy indefinitely after achieving remission. Nevertheless, many trials (European Stop TKI Study EURO-SKI, STIM1, ENEST freedom, ENESTop, DADI) showed promising results with successful TKI discontinuation. It is still not determined if this ''TKI break'' affects the survival benefit. When clinicians decide to withhold the TKIs, they must adequately and correctly select the patients: chronic phase CML without a prior history of accelerated or blast phase CML, being on TKI for at least 3 years with an evidence of stable molecular response (MR4; BCR-ABL ≤0.01%) for more than 2 years, not having a history of resistance to any TKI. Patients should do a monthly molecular monitoring for the first six months following discontinuation, then bi-monthly for the next 6 months, then every 3 months.

In conclusion, CML remains a challenging disease with improved outcome compared to the pre-TKIs era. In the chronic phase - CML, clinicians have many choices to prescribe as a first line treatment. In case of treatment intolerance, the patients can be switched to another TKI. Relapsing or resistant disease with T315I mutation may benefit from Ponatinib. The Allogeneic Hematopoietic stem cell transplantation (HSCT) is considered in the case of failure of two TKIs, but it remains the only curative treatment opposed to the TKIs.