Decision making in hematology—chronic myeloid leukemia

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Summary Chronic myeloid leukemia is nowadays associated with a good prognosis and an excellent life expectancy. However, certain levels of responses have to be achieved with the various available tyrosine kinase inhibitors at certain time points during the treatment otherwise adequate diagnostic and therapeutic actions have to be initiated. This paper will focus on these issues.

Keywords Tyrosine kinase inhibitor · CML · Chronic phase · Therapeutic management · Treatment outcome

Introduction

Chronic myeloid leukemia (CML) has transformed from a disease that led to death within a median of about 5 years for the majority of patients in earlier years to a chronic disease with an almost normal life expectancy compared to the general population [1]. This dramatic change was caused by the introduction of the tyrosine kinase inhibitor (TKI) imatinib [2, 3], the subsequently generated 2nd generation (2ndG) TKIs dasatinib [4], nilotinib [5], bosutinib [6] and the 3rdG TKI ponatinib [7]. In order to be able to maintain the chronic phase (CP) of the disease during the whole life span of individual patients important decisions have to be made at the time of diagnosis as well as at certain points of time thereafter.

Decision 1: Which TKI to start with?

All currently available 2ndG TKIs (bosutinib, dasatinib, nilotinib) were compared to imatinib in several phase 3 studies in CP CML patients and have demonstrated that major molecular remissions (MMR, also termed MR3) or deeper molecular remissions (DMR; i.e., MR4 and MR4.5, respectively) are achieved at higher frequencies and more rapidly with 2ndG TKIs compared to imatinib [4–6]. Moreover, transformations from CP into accelerated phase (AP) or blast crisis (BC) were also seen less frequently with 2ndG TKIs. Overall, all these putative benefits, however, did not transform into a significantly improved progression-free (PFS) and overall survival (OS) benefit [4–6]. Reasons for this are mainly that 2ndG TKIs have sometimes more severe (including organ damaging) side effects that were not known well enough at the time the studies were performed and that the studies were also not powered to demonstrate a possibly small OS benefit if any at all. The decision for imatinib (including generic imatinib) or a 2ndG TKI at diagnosis, therefore, has to be made on the basis of age, coexisting comorbidities in the context of possible side effects of the various TKIs and risk scores as patients with high risk based on Sokal, European Treatment and Outcome Study for CML (EUTOS) or EUTOS long-term survival (ELTS) score (which nowadays should be used based on the most recent recommendations of the European Leukemia NET (ELN) [8]) reveal the greatest benefit in terms of therapeutic failure or progression of the disease into more advanced phases (i.e., AP or BC) [2–6].

In addition, another important issue has to be discussed with the patient early on, namely, how important it may be for the patient to achieve a DMR in order to be able to subsequently potentially stop the TKI therapy for a longer period of time. If treat-

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ment discontinuation is a major goal, a 2ndG TKI should be preferred over imatinib if no other factors speak against its use [3–6, 8]. In case of AP at diagnosis, a 2ndG TKI or even a 3rdG TKI should be used and chosen based on comorbidities and a possibly already existing BCR-ABL kinase mutation [8]. If CML presents in BC at diagnosis, 2ndG or 3rdG TKIs are either used as single agents [9–11] or in combination with chemotherapeutic agents known for the treatment of acute leukemias [12, 13] or hypomethylating agents [14, 15].

Decision 2 at month 3–6: Did your patient achieve a sufficiently good response?

After starting TKI treatment, blood cell counts including differential blood counts should be performed every other week until a complete hematological response is achieved. At 3 months and every 3 months thereafter (at least until achieving a MMR or MR3), a quantitative measurement of BCR-ABL on blood cells according to the international scale (BCR-ABL^{IS}) should be done [8]. Ideally, a BCR-ABL^{IS} of $\leq 10\%$ should be achieved after 3 months to be termed “optimal response”. If a value of BCR-ABL^{IS} of $> 10\%$ is confirmed within the next following 3 months, TKI therapy must be changed to an alternative TKI. If a mutation within the BCR-ABL kinase is detected under these circumstances, the following TKI must be sensitive to the detected mutation. In case of the availability of various sensitive TKIs, the best suitable TKI according to existing comorbidities can be chosen. If no BCR-ABL kinase mutation is detected, any other available TKI can be taken. In the case that the initial CML therapy was started with imatinib, this should be a 2ndG TKI. If, however, CML therapy was already started with a 2ndG TKI, one should strongly consider using the 3rdG TKI ponatinib if no cardiovascular risk factors preclude its use [8], as data from the 3rd line setting strongly suggest a low likelihood of a long-term response of a 2ndG TKI after a 2ndG TKI [16]. In contrast to the initially FDA (US Food and Drug Administration) approved dose of 45 mg per day, the 2020 ELN guidelines strongly recommend to start with a lower dose of 30 mg or even 15 mg to avoid cardiovascular toxicity except in patients with T315I, compound mutations or progression to an advanced phase [8]. This suggestion from the ELN is supported in part from recent results of the OPTIC study, showing that a starting dose of 30 mg ponatinib is equally effective to the 45 mg dose if no mutation is present or if ≤ 2 prior TKIs were used. Moreover, the study also revealed that the ponatinib dose can be further reduced to 15 mg if a BCR-ABL^{IS} value of $\leq 1\%$ is achieved [17].

The same considerations have to be performed if BCR-ABL^{IS} values of $> 1\%$ are measured at 12 months or any time thereafter.

In case of intolerance, every other available TKI can be considered.

Decision 3: Can I stop TKI therapy safely?

Stopping the treatment in CP CML patients is of major interest. Several studies have demonstrated that stopping TKI therapy is safe under certain circumstances [18, 19]. These include patients in 1st CP (including a change of TKI treatment in case of intolerance) that have achieved a DMR defined as BCR-ABL1 levels of at least MR⁴ or deeper on the IS, a duration of DMR > 2 years (in case of MR⁴ duration should be > 3 years), a duration of TKI therapy for at least 5 years in case of imatinib and 4 years for 2ndG TKIs and no prior treatment failure [8, 18, 19]. In case of stopping TKI therapy, patients must be monitored more frequently (monthly for the first 6 months, every other month for months 6–12) during the first 12 months as more than 80% of molecular recurrences occur during this time period, the vast majority in the first 6–8 months. If MMR or MR3 is lost, patients can restart therapy with the same TKI if no prior experienced side effects speak against it [8].

Decision 4: When should allogeneic stem cell transplantation be considered?

Before the introduction of TKI therapy, allogeneic stem cell transplantation was a major goal and the only curative option in CML therapy for suitable patients, ideally performed within the first year on interferon therapy [20]. This has changed dramatically since the use of the various TKIs became available for the management of CML. Nowadays, allogeneic stem cell transplantation should be strongly considered in all eligible CP CML patients in case of failure to ≥ 2 TKIs and a donor search should be initiated [8]. In addition, patients progressing to AP or BC during TKI therapy as well as patients in AP or BC at diagnosis are candidates for allogeneic transplantation, which should be performed whenever possible. An attempt to return the patients into a 2nd CP with 2nd or 3rdG TKIs should be made as the outcome with allogeneic transplantation improves strongly under this circumstance [21].

Take home message

The major goal of today's management of CP CML with TKIs is to maintain the patients in CP of the disease. To achieve this goal, important points in the therapeutic management of the disease have to be considered. These are as follows:

- Choice of TKI at diagnosis
- Timely change to an appropriate TKI in case of therapeutic failure
- Considering the option of allogeneic stem cell transplantation
- Considering a safe timepoint for TKI discontinuation

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References

1. Bower H, Björkholm M. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. *J Clin Oncol*. 2020; <https://doi.org/10.1200/JCO.2015.66.2866>.
2. O'Brien SG, Guilhot F. Imatinib compares with interferon and low-dose Cytarabine for newly diagnosed chronic-phase myeloid leukemia. *N Engl J Med*. 2003; <https://doi.org/10.1056/NEJMoa022457>.
3. Hochhaus A, Larson RA. Long-term outcomes of Imatinib treatment for chronic myeloid leukemia. *N Engl J Med*. 2017; <https://doi.org/10.1056/NEJMoa1609324>.
4. Kantarjian H, Shah NP. Dasatinib versus Imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010; <https://doi.org/10.1056/NEJMoa1002315>.
5. Saglio G, Kim DW. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010; <https://doi.org/10.1056/NEJMoa0912614>.
6. Cortes JE, Gambacorti-Passerini C. Bosutinib versus Imatinib for newly diagnosed myeloid leukemia: results from the randomized BFORE trial. *J Clin Oncol*. 2018; <https://doi.org/10.1200/JCO.2017.74.7162>.
7. Cortes JE, Kim DW. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood*. 2018; <https://doi.org/10.1182/blood-2016-09-739086>.
8. Hochhaus A, Baccarani M. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia*. 2020; <https://doi.org/10.1038/s41375-020-0776-2>.
9. Guilhot F, Apperley J. Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. *Blood*. 2007; <https://doi.org/10.1182/blood-2006-09-046839>.
10. Cortes J, Rousselot P. Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. *Blood*. 2007; <https://doi.org/10.1182/blood-2006-09-046888>.
11. Cortes JE, Kim DW. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2013; <https://doi.org/10.1056/NEJMoa1306494>.
12. Strati P, Kantarjian H. HCVAD plus imatinib or dasatinib in lymphoid blastic phase chronic myeloid leukemia. *Cancer*. 2014; <https://doi.org/10.1002/cncr.28433>.
13. Fruehauf S, Topaly J. Imatinib combined with mitoxantrone/etoposide and cytarabine is an effective induction therapy for patients with chronic myeloid leukemia in myeloid blast crisis. *Cancer*. 2007; <https://doi.org/10.1002/cncr.22535>.
14. Ghez D, Micol JB. Clinical efficacy of second generation tyrosine kinase inhibitor and 5-azacytidine combination in chronic myelogenous leukemia in myeloid blast crisis. *Eur J Cancer*. 2013; <https://doi.org/10.1016/j.ejca.2013.07.147>.
15. Sauße S, Silver RT. Management of chronic myeloid leukemia in blast crisis. *Ann Hematol*. 2015; <https://doi.org/10.1007/s00277-015-2324-0>.
16. Jabbour E, Kantarjian H. Use of second- and third-generation tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia: an evolving treatment paradigm. *Clin Lymphoma Myeloma Leuk*. 2015; <https://doi.org/10.1016/j.clml.2015.03.006>.
17. Cortes J, Hughes TP. Asciminib, a first-in-class STAMP inhibitor, provides durable molecular response in patients (pts) with chronic Myeloid leukemia (CML) harboring the T315I mutation: primary efficacy and safety results from a phase 1 trial. *Blood*. 2020;136(Supplement 1):47–50. <https://doi.org/10.1182/blood-2020-139677>.
18. Campiotti L, Suter MB. Imatinib discontinuation in chronic myeloid leukemia patients with undetectable BCR-ABL transcript level: a systematic review and a meta-analysis. *Eur J Cancer*. 2017; <https://doi.org/10.1016/j.ejca.2017.02.028>.
19. Sausse S, Richter J. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukemia (EURO-SKI): a pre-specified interim analysis of a prospective, multicentre, non-randomised, trial. *Lancet Oncol*. 2018; [https://doi.org/10.1016/S1470-2045\(18\)30192-X](https://doi.org/10.1016/S1470-2045(18)30192-X).
20. Silver RT, Woolf SH. An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of Myeloid leukemia: developed for the American society of hematology. *Blood*. 1999;94(5):1517–36.
21. Sausse S, Lauseker M. Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. *Blood*. 2010; <https://doi.org/10.1182/blood-2009-08-237115>.

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