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COMMENTARY

Tyrosine kinase inhibitors (TKIs) used in the management of chronic myeloid leukaemia are associated with haematologic toxicities—Which TKI is the safest?

Before imatinib, patients with chronic myeloid leukaemia (CML) received hydroxycarbamide, or interferon-alpha alone or in combination with low-dose cytarabine. Younger and fit patients with a suitable donor could be allografted, which was the only potentially therapeutic approach that would result in long-term disease-free survival; however, substantial morbidities or even mortality was observed.

The discovery of tyrosine kinase inhibitors (TKIs) against the *BCR-ABL1* oncogenic fusion protein has revolutionized the management of CML. Imatinib, the first *BCR-ABL1* TKI, was introduced in early 2000s, and in the upcoming years, more potent second-generation TKIs (2GTKIs)—dasatinib, nilotinib, and bosutinib—have been approved, first for the imatinib resistant/intolerant cases and subsequently for the upfront treatment.[1] Although not globally approved, another 2GTKI—radotinib—is currently approved for both the frontline and salvage settings in Korea.[2] Other than these TKIs, ponatinib is a third-generation TKI, an option in patients with CML who fail two lines of TKI treatment and in those harbouring a T315I mutation.

Imatinib therapy can be associated with some adverse events (AEs), both haematologic and non-haematologic, which are generally easy to manage, but sometimes, they may have a negative impact on the health-related quality of life (HRQoL).[3] The newer TKIs generally induce more rapid and profound responses than imatinib; however, these drugs can also be associated with additional specific non-haematologic toxicities resulting in morbidities that might interfere with patient HRQoL.[4]

Overall, haematologic toxicities (myelosuppression) during TKI treatment is quite common, and it occurs both due to the suppression of the leukemic clone and the inhibition of non-leukemic haematopoiesis.[5] When leukemic haematopoiesis is reduced by the TKI treatment, normal stem and progenitor cells need time to recover from pre-existing suppression by the malignant clone and to re-populate the bone marrow. Myelosuppression is usually limited to the first weeks or months of TKI therapy, and the incidence of grade III-IV myelosuppression is usually predominant only at the initial phase of the TKI treatment, decreasing substantially with longer duration of any TKI therapy.

Haematologic AEs of TKIs are mostly dose and concentration dependent, reversible on treatment cessation or dose reduction, and affect all three lineages to a variable degree.[5] Thus, myelosuppression is an expression of exposure of the consumed TKI. It is important, because it is the major cause of temporary and/or permanent cessation of the TKI.

In this issue of the *British Journal of Clinical Pharmacology*, Fachi and coworkers performed a systematic review and a meta-analysis on the serious (grade III-IV) haematologic AEs (anaemia, leukopenia, neutropenia, and thrombocytopenia) of all TKIs (imatinib, dasatinib, nilotinib, bosutinib, radotinib, or ponatinib, at any dose or regimen) utilized in the management of CML in chronic phase (CML-CP) focusing on the randomized controlled trials (RCTs) mainly included newly diagnosed and treatment naïve patients.[6]

After the initial evaluation, the authors included 17 trials for the final analysis. As expected, none of the trials were placebo controlled, majority of them were sponsored by pharmaceutical companies, and all of the studies were open-label and with direct *head-to-head comparison*, including all TKIs (bosutinib [n = 2], dasatinib [n = 5], imatinib [n = 16], nilotinib [n = 4], ponatinib [n = 1], and radotinib [n = 1]).[6] Imatinib was the main comparator in all trials but one, in which different doses of dasatinib were tested in the second-line setting among cases with CML-CP following imatinib failure/intolerance.[7]

Although dose equivalence between these agents is unclear, the authors demonstrated that doses above 100-mg dasatinib caused anaemia in significantly more patients than that caused by imatinib up to 600 mg/day, or 600-mg nilotinib. However, there was no significant difference between dasatinib 100 mg and imatinib 400 mg (the recommended daily doses in newly diagnosed CML-CP cases) regarding the number of cases with grade III-IV anaemia. Supporting this finding, in the DASISION trial, where dasatinib 100 mg was tested against imatinib 400 mg in the first-line setting among patients with CML-CP, the percentages of grade III-IV anaemia were found to be 10% and 7% for dasatinib and imatinib, respectively.[5]

Similarly, when the authors compared all TKIs that are approved in the upfront setting in CML-CP with the recommened daily doses (imatinib 400 mg/day, nilotinib 600 mg/day, dasatinib 100 mg/day, bosutinib 400 mg/day, and radotinib 600 mg/day) with each other, there were no significant differences between these TKIs at those doses for the generation of grade III-IV anaemia.[6]

Both dasatinib 100 and 140 mg and imatinib 400 and 800 mg caused more leukopenia than nilotinib daily doses of 600 or 800 mg.

Although dasatinib 140 mg/day significantly caused more neutropenia than nilotinib 600 or 800 mg and ponatinib 45 mg, bosutinib 400 mg daily caused significantly more neutropenia than dasatinib 140 mg. If all TKIs approved for the upfront setting with the recommended daily doses were compared with each other, no significant differences between each other regarding the development of leukopenia or neutropenia were detected.[6]

Regarding thrombocytopenia, 140-mg dasatinib was the less safe option, imatinib (400-600 mg) and 600-mg radotinib presented the lowest probabilities of causing this event.[6] When all TKIs approved for the upfront setting were compared with each other for the recommended daily doses, dasatinib 100 mg had significantly more cases with thrombocytopenia than imatinib 400 mg/day, but no such significant difference was observed between other TKIs. This is consistent with the finding in the DASISION trial, with grade III-IV thrombocytopenia in the dasatinib and imatinib arms were 19% and 10%, respectively.[5]

Although the authors found that myelosuppression was typically more frequent with dasatinib administered in both doses (100 and 140 mg), significant difference was observed between dasatinib 140 mg and the other TKIs. Dasatinib 140 mg is not the recommended starting daily dose in patients with CML-CP, and dose can be increased in CMP-CP when there is a suboptimal response under dasatinib 100 mg. What's more, recently, a lower daily dose (50 mg) of dasatinib was found to be equally effective to those observed under dasatinib 100 mg/day,[8] although some questions remain unanswered.[9] In this study, three out of 75 patients receiving 50 mg/day had a dose interruption for ≤14 days in the first 3 months of therapy due to thrombocytopenia, and all of them restarted the TKI therapy with the same dose without experiencing any toxicities.[8] The effect of exposure on efficacy and toxicity was not measured however, likely known variability between dose and exposure, and clear relationship of exposure to efficacy and toxicity could explain such outcome.[10]

Taken all haematologic toxicities together and considering only the RCTs that assessed newly diagnosed CML cases, 400-mg imatinib was demonstrated to be safer than 400-mg bosutinib (OR 0.40 with 95% CrI [0.17-0.90]), 100-mg dasatinib (OR 0.50 with 95% CrI [0.27-0.84]), and 800-mg imatinib (OR 0.47 with 95% CrI [0.32-0.71]). In the upfront setting, 600-mg nilotinib presented a 27% probability of being the least safe drug of choice.[6]

The most common 2GTKIs used in the daily clinical practice are dasatinib and nilotinib, and literature shows conflicting results regarding the toxicity profiles of these two 2GTKIs. For example, in the multicenter observational study by Kizaki and colleagues,[11] the grade ≥III haematologic AEs (anaemia, neutropenia, and thrombocytopenia) were all significantly more common with dasatinib than those with imatinib and nilotinib, when these TKIs were used as a first-line treatment in patients with CML-CP. However, this was not the case in the retrospective Japanese study of Ota et al,[12] and the percentages of grade III-IV haematologic toxicities for upfront imatinib, dasatinib, and nilotinib were 14.5%, 14.7%, and 13%, respectively, among CML-CP patients. In another study, the authors conducted a propensity score matched comparison of patients with CML-CP who received frontline therapy with either dasatinib (n = 107; 100 mg/day) or nilotinib (n = 104; 800 mg/day) from two single-arm, single-institution phase II trials.[13] Besides showing similar response and survival outcomes, frontline dasatinib and nilotinib therapies were comparable regarding all grade ≥III haematologic toxicities (anaemia, neutropenia, and thrombocytopenia).

TKI therapy is not without toxicities, and patients may experience haematologic and non-haematologic AEs during TKI treatment, which require proper management. Relationships between dose and side effects are often complex, particularly as the side effects are now documented to be significnatly related to exposure,[14] which may not so clearly be related to dose. Further, with respect to the haematologic side effects of TKIs, the dose-response curves for harm and therapeutic effect are superimposed, and therefore adverse reactions collateral, at least initially.[15] As the authors stated, haematologic toxicities may require temporary treatment interruption or dose reductions, which sometimes lead to treatment discontinuation, non-adherence to TKI therapy, resulting in reduced exposure, and can also be associated with a lower probability of achieving optimal responses. Routine pharmacokinetic and pharmacodynamic modelling of drug serum concentrations and haematologic parameters might provide us with additional insight in how to optimize treatment. In addition, some of the earlier described observations might also be related to the actual systemic exposure rather than the dose, and assessing the systemic exposure to these drugs might therefore help to manage the balance between efficacy and toxicity in individual patients.[14,16] Following their analysis, Fachi et al[6] demonstrated that dasatinib appeared to be the least safe TKI for CML regarding grade ≥III haematologic AEs. However, there are conflicting results from the literature. Patients enrolled in the RCTs do not always reflect the general population, since patients with significant comorbidities are excluded from these clinical trials. So therefore, rates of haematologic toxicities for each TKI observed in "real life" might differ from those observed in clinical trials. Future careful studies with these drugs that include a clinical pharmacology component could inform us how to further optimize the use of these drugs in real-life patient care.

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REFERENCES

1. Eşkazan AE. Evolving treatment strategies in CML—moving from early and deep molecular responses to TKI discontinuation and treatment-free remission: is there a need for longer-term trial outcomes? *Br J Clin Pharmacol*. 2018;84(8):1635-1638.
2. Eskazan AE, Keskin D. Radotinib and its clinical potential in chronic-phase chronic myeloid leukemia patients: an update. *Ther Adv Hematol*. 2017;8(9):237-243.
3. Kirkizlar O, Eskazan AE. Adverse events of tyrosine kinase inhibitors and their impact on quality of life in patients with chronic myeloid leukemia. *Expert Review of Quality of Life in Cancer Care*. 2016;1(5):353-359.
4. Eskazan AE, Ozmen D. Tyrosine kinase inhibitor (TKI) therapy for newly-diagnosed patients with chronic myeloid leukemia: focusing on TKI discontinuation due to adverse events—is better always good? *Expert Rev Hematol*. 2017;10(7):583-586.
5. Steegmann JL, Baccarani M, Breccia M, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. *Leukemia*. 2016;30(8):1648-1671.
6. Fachi MM, Tonin FS, Leonart LP, Rotta I, Fernandez-Llimos F, Pontarolo R. Haematological adverse events associated with tyrosine kinase inhibitors in chronic myeloid leukemia: a network meta-analysis. *Br J Clin Pharmacol*. 2019;85(10):2280-2291.
7. Shah NP, Kim DW, Kantarjian H, et al. Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. *Haematologica*. 2010;95(2):232-240.
8. Naqvi K, Jabbour E, Skinner J, et al. Early results of lower dose dasatinib (50 mg daily) as frontline therapy for newly diagnosed chronic-phase chronic myeloid leukemia. *Cancer*. 2018;124(13):2740-2747.
9. Eskazan AE. Starting with a lower daily dose of dasatinib in patients with chronic myeloid leukemia in chronic phase: less is more, or is it? *Cancer*. 2018;124(21):4260-4261.
10. Lucas CJ, Dimmitt SB, Martin JH. Optimising low dose methotrexate for rheumatoid arthritis—a review. *Br J Clin Pharmacol*. 2019;85(10):2228-2234.
11. Kizaki M, Takahashi N, Iriyama N, et al. Efficacy and safety of tyrosine kinase inhibitors for newly diagnosed chronic-phase chronic myeloid leukemia over a 5-year period: results from the Japanese registry obtained by the New TARGET system. *Int J Hematol*. 2019;109(4):426-439.
12. Ota S, Matsukawa T, Yamamoto S, et al. Severe adverse events by tyrosine kinase inhibitors decrease survival rates in patients with newly diagnosed chronic-phase chronic myeloid leukemia. *Eur J Haematol*. 2018;101(1):95-105.
13. Takahashi K, Kantarjian HM, Yang Y, et al. A propensity score matching analysis of dasatinib and nilotinib as a frontline therapy for patients with chronic myeloid leukemia in chronic phase. *Cancer*. 2016;122(21):3336-3343.
14. Krens SD, Lassche G, Jansman FGA, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol*. 2019;20(4):e200-e207.
15. Ferner R, Aronson J. Susceptibility to adverse drug reactions. *Br J Clin Pharmacol*. 2019;85(10):2205-2212.
16. Martin JH, Dimmitt S. The rationale of dose-response curves in selecting cancer drug dosing. *Br J Clin Pharmacol*. 2019;85(10):2198-2204.

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