Optimization of CML therapy using TDM

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Imatinib mesylate, a tyrosine kinase inhibitor (TKI) of the BCR–ABL fusion protein, has demonstrated significant clinical efficacy in the treatment of Philadelphia (Ph) chromosome-positive chronic myeloid leukemia (CML). Second-generation TKIs, including nilotinib, dasatinib, and bosutinib, or third-generation TKI, ponatinib have been developed to counter imatinib resistances associated with BCR-ABL1 mutations. Nilotinib and dasatinib, have already been approved as a first-line treatment for CML in many countries.

According to European LeukemiaNet recommendation, the clinical response of CML patients receiving TKI therapy should be evaluated after 3, 6, 12 months and thereafter. For patients not achieving a optimal response by these time-points, the baseline presence or later emergence of BCR-ABL1 mutations or other genetic variants, and pharmacokinetic (PK) factors, such as PK-related inter-individual variation affecting metabolism and drug–drug interactions and the patient’s compliance with therapy should be considered.

The plasma concentration of TKI might be a great help to dosage optimization or switching TKI. The imatinib plasma trough concentration (C₀) should be set above 1,000 ng/mL to obtain a response and below 3,000 ng/mL to avoid serious adverse events such as neutropenia. For patients with a UGT1A1*6/*6, *6/*28, or *28/*28 genotype initially administered 300–400 mg/day, a target nilotinib C₀ of 500 ng/mL is recommended to prevent elevation of bilirubin levels, whereas for patients with the UGT1A1*1 allele initially administered 600 mg/day, a target nilotinib C₀ of 800 ng/mL is recommended. For dasatinib, it is recommended that a higher C_max or C₂ (above 50 ng/mL) to obtain a clinical response and a lower C₀ (less than 1.5 ng/mL) to avoid pleural effusion be maintained by once daily administration of dasatinib. For bosutinib, a target C₀ of less than 100 ng/mL is recommended to avoid serious adverse events, such as diarrhea or liver dysfunctions. There are significant correlation between dosage of ponatinib and vascular adverse events (VAEs). It might be set below a target ponatinib C₀ to avoid severe VAEs by therapeutic drug monitoring (TDM). A target C₀
of 23 ng/mL (40 nM) is recommended according to the result of IC$_{50}$ values by in vitro assay. In our experiences, the median values of concentration was 24.6 ng/mL (95%CI: 23.0-29.3 ng/mL) and 48.0 ng/mL (43.7-53.3 ng/mL) in patients treated by ponatinib 15 mg QD (n=30) and 30 mg QD (n=15), respectively.

In conclusion, TDM might be a new strategy to obtain safely a faster and more effective clinical response in TKI therapy for CML patients.