Pharmacogenetics in patients with childhood acute lymphoblastic leukemia

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Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. In the past few decades, the therapeutic outcome of ALL has achieved remarkable progression, with 5-year overall survival reaching >90%. Despite this improvement in therapeutic outcome, treatment-related severe toxicity results in interruption of therapy consequently compromising efficacy. Therefore, the prediction of response to therapy and appropriate adjustment of therapeutic dose is important to further improve the therapeutic outcome. Host inherited genetic variant may be a predictive factor of therapeutic response.

The agent 6-mercaptopurine (6-MP) is the main component of ALL therapy. However, a proportion of ALL patients experience severe toxicity and require interruption of therapy. Established factors of 6-MP sensitivity include a germline genetic variation and low expression of a drug metabolite enzyme termed thiopurine S-methyl transferase (TPMT). However, the frequency of TPMT deficiency among Asian patients is lower than that observed among European patients. Therefore, *TPMT* genotyping has not been useful in the Asian population for the adjustment of the therapeutic dose. Recently, a genome-wide association study revealed that the variant of *nudix hydrolase 15* (*NUDT15*) was a risk factor of 6-MP intolerability. Thereafter, studies reported the association between the *NUDT15* genotype and 6-MP tolerability or therapeutic outcome in mainly Asian patients with childhood ALL. *NUDT15* codes the NUDT15 enzyme, which dephosphorylates thioguanosine triphosphate to monophosphate. Patients with the *NUDT15* variant are highly sensitive to 6-MP. In particular, patients with the homozygous variant require reduction of the 6-MP dose to <10 mg/m^2/day during maintenance therapy. Notably, the tolerable dose of 6-MP for patients with the *NUDT15* homozygous variant was different than that reported in those with the *NUDT15* diplotype. Furthermore, 6-MP tolerability is influenced by the interaction with other risk variants, such as transporters. In Asia, in the near future, the initial dose of 6-MP will be adjusted according to the patient's *NUDT15* genotype. In this lecture, I will discuss the pharmacogenetics of childhood ALL, especially 6-MP tolerability associated with germline *NUDT15* variant.