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Contribution of the β-ureidopropionase (*UPB1*) gene alterations to the development of fluoropyrimidine-related toxicity

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Abstract:
Background: An impairment of the 5-fluorouracil (5-FU) catabolic pathway, represented by alterations in the dihydropyrimidine dehydrogenase (DPYD) gene, is considered a crucial factor contributing to the development of 5-FU-related toxicity. The β-ureidopropionase (BUP1) enzyme catalyzes the final step in the 5-FU catabolic pathway; however, alterations in the *UPB1* gene coding for the BUP1 enzyme have not yet been analyzed in fluoropyrimidine (FP)-treated patients suffering from 5-FU-related toxicity.
Methods: We have performed a mutation analysis of the entire coding sequence of *UPB1* based on denaturing high-performance liquid chromatography in 113 cancer patients treated by FP-containing regimes. These patients included 67 individuals suffering from severe 5-FU-related toxicity and 46 individuals with excellent tolerance of chemotherapy.
Results: Nine *UPB1* variants were detected in the subpopulation of patients with severe toxicity, including a novel mutation affecting the coding sequence (c.872_873+11del13). An analysis of *UPB1* variants on 5-FU-related toxicity in the population of all analyzed patients revealed an association between the c.-80C>G (rs2070474) variant and gastrointestinal toxicity. A strong positive correlation was found between the carriers of the c.-80 GG genotype and the development of severe (grade 3–4) mucositis (OR = 7.5; 95% CI = 2.60 – 21.60; p = 0.0002).
Conclusion: Our results suggest that *UPB1* variants may contribute to the development of 5-FU-related toxicity in some FP-treated patients; however, the role of *UPB1* alterations is probably less significant than that of *DPYD* alterations.

Key words:
β-ureidopropionase (UPB1), β-alanine synthase, 5-fluorouracil, fluoropyrimidines, denaturing high-performance liquid chromatography (DHPLC), toxicity