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Thymidilate Synthase Polymorphisms in Indonesian Childhood Acute Lymphoblastic Leukemia

Abstract

The enzyme thymidylate synthase (TS) converts dUMP into dTMP and requires folates as co-factors. Since dTMP is necessary for DNA synthesis, TS is an important target of cancer chemotherapy. Ethnic variations of the polymorphic tandem repeat sequence in the enhancer region of the TS promoter, has previously been described to influence the outcome of acute lymphoblastic leukaemia (ALL). A triple repeat is associated with a higher TS gene expression than a double repeat, resulting in poorer outcome of ALL patients treated with the anti-folate methotrexate (MTX). In addition, the association of TS expression and MTX resistance appears to be even more pronounced in combination with an accumulation of folates. This latter event can occur when methylenetetrahydrofolate reductase (MTHFR) has impaired enzyme activity due to a C667T mutation. In this study, we determined the ethnic variations of the TS and MTHFR genotype between Caucasian and Indonesian in ALL cells obtained at diagnosis from 157 Caucasian and 101 Indonesian children with MTX-treatment in prospective. Furthermore, we determined the involvement of TS polymorphisms in MTX sensitivity, by using a TS inhibition assay (TSIA). Homozygous TS triple repeats were more than twice as common in Indonesian samples (76.3%) than in Caucasian samples (33.1%). Heterozygotes of the MTHFR mutations were seen in 15% of the screened Indonesian samples. These results demonstrate significant ethnic variation in a TS gene regulatory element in leukemic cells. A difference was found between the MTX sensitivity and the presence of a double or triple repeat in the Caucasian ALL group. Interestingly, according to these data it seems that the samples with a triple repeat show a shift in their distribution towards hypersensitivity to MTX, in contrast to previously described results. However four of the samples (16.0%) did show resistance to MTX, which may suggest an additional role for other enzymes, such as MTHFR. Further investigation in the Indonesian samples may give insight in the role of the polymorphisms in MTX sensitivity.


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