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承認から臨床への安全な導入—現場での対応—**
—イリノテカン：現場より—

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Genotype-Based Irinotecan Chemotherapy: Introducing Pharmacogenetics into Clinical Practice

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Summary

Irinotecan, a camptothecin analogue with strong antitumor activity via inhibition of topoisomerase I, has been widely used to treat many cancers, though it sometimes causes severe neutropenia and diarrhea. Further, the active metabolite of irinotecan, SN-38, is inactivated by UDP-glucuronosyltransferase (UGT) 1A1 enzyme, which shows genetically polymorphic functions, resulting in marked interindividual variations in susceptibility to irinotecan chemotherapy. When cancer patients who carry variant *UGT1A1* alleles receive irinotecan, their low SN-38 glucuronidating activity causes unexpected accumulation of the active metabolite in the body and this may increase the drug toxicity. Therefore, when patients are known to have variant *UGT1A1* alleles, it is a reasonable clinical option to use a lower initial dosage or to switch to other drug regimens to avoid irinotecan use. Careful examination for toxicity after irinotecan administration is needed for these patients at higher risk of adverse effects. Genetic testing of *UGT1A1*28*, a polymorphism with a 2-base pair insertion (TA) within the promoter $(TA)_6$ TAA, resulting in the variant sequence $(TA)_7$ TAA, has been approved in the United States for predicting the toxicity of irinotecan. Testing of *UGT1A1*6*, a single nucleotide polymorphism existing in exon 1 that is found almost exclusively in Asians, has recently been introduced into clinical practice in Japan. For Asian patients, *UGT1A1*6* should be genotyped together with *UGT1A1*28* to allow for more appropriate individualized chemotherapy with irinotecan.

Key words

Irinotecan, SN-38, Toxicity, UGT1A1, Polymorphism