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Pharmacogenetics to predict adverse drug reactions in oncology: distant goal or reality?

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Background

Drug pharmacokinetics and pharmacodynamics are controlled, at the individual level, by genetic factors and pharmacogenetics is the discipline that provides the theoretical and scientific basis of intersubject variability of drug responses. The ability to select patients on the basis of the likelihood of toxicity caused by a chemotherapeutic agent would avoid the empiricism dependent on the inability to match the most appropriate drug with the specific genetic profile of the patient. Our increasing knowledge of the mechanisms of drug action, the identification of new targets and the understanding of genetic factors that determine the response to drugs of individual patients may allow the design of treatments that target specific tumours or minimize the intersubject variation in drug tolerability. Examples of genetic variability affecting drug inactivation are dihydropyrimidine dehydrogenase for fluoropyrimidines and UDP-glucoronosyl-transferase for irinotecan. Therefore, genetic analysis has the potential to predict treatment efficacy and tolerability. However, major problems encountered in pharmacogenetic studies are the need of extensive clinical validation of available technology, the difficulties in obtaining a suitable amount of sample from patients and the complex regulation of gene function.

5-FU and fluoropyrimidines

Since the initial clinical use of 5-FU and derivatives, it was evident that some patients suffered from severe toxicities, suggesting that genetic factors were responsible for these differences. Dihydropyrimidine dehydrogenase (DPD) is the rate-limiting enzyme of 5-FU catabolism and 85% of a dose of 5-FU is inactivated by the DPD. Therefore, a genetically-dependent enzyme deficiency is associated with a profound alteration of drug metabolism and severe toxicities. The more common genetic variants of DPD associated with severe toxicities are c.1905+1G>A and c.2846A>T, which encode for an inactive enzyme (1). These genetic variants are present in approximately 5% of individuals (2) and, therefore, DPD genotyping turns out to be a useful pharmacogenetic test for the identification of patients at risk of life-threatening toxicities.

Irinotecan

Cleavage of the bispiperidine moiety of irinotecan by carboxylesterases releases the active metabolite SN-38, which is up to 1000 times more potent than the parent compound in inhibiting nuclear topoisomerase I. The isoform 1A1 of the enzyme uridine diphosphate-glucuronosyl transferase (UGT1A1) plays a pivotal role in SN-38 detoxification, leading to the formation of the inactive metabolite SN-38 glucuronate (SN-38G) (3). The rate of SN-38 glucuronidation is genetically determined and variants of UGT in poor-metabolizers have been described, thus providing the potential reason of severe neutropenia and dose-limiting diarrhea suffered by some patients. The most common cause of reduced glucuronidation is a polymorphism of the promoter region of UGT1A1

consisting of the presence of a variable number of TA tandem sequences (4). Individuals with higher number of TA repeats, i.e., TA_7 (UGT1A1*28), have reduced gene expression and diminished UGT1A1 production than wild type TA_6 (UGT1A1*1) (5). Additional nucleotide changes in the UGT1A1 gene generate a number of variants with reduced activity (UGT1A1*6, UGT1A1*7, UGT1A1*27, UGT1A1*29) (6). Other UGT isoforms involved in irinotecan metabolism also show missense mutations with moderate to profound reduction in UGT activity, including Met33Thr Asp256Asn in UGT1A9 (7, 8) and Trp208Arg, Asn129Lys and Arg131Lys in UGT1A7 [46]. Finally, the influence of irinotecan oxydation to 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxy-camptothecin (APC) and to 7-ethyl-10-(4-amino-1-piperidino)-carbonyloxy-camptothecin (NPC) by CYP3A4 and its genetic variants adds additional complexity to the issue (9).

Conclusions

There are solid evidences that, in selected cases, pharmacogenetics is a valid approach to identify subjects at risk of severe toxicities and should be implemented in clinical practice and as a selection criterion in clinical trials as well.

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