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Invited review

UGT genotyping in belinostat dosing

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ABSTRACT

Certain genetic polymorphisms of UDP glucuronosyltransferase 1 family, polypeptide A1 (*UGT1A1*) can reduce gene expression (**28*, **60*, **93*) or activity (**6*), thereby altering the pharmacokinetics, pharmacodynamics, and the risk of toxicities of UGT1A1 substrates, of which irinotecan is a widely-described example. This review presents an overview of the clinical effects of *UGT1A1* polymorphisms on the pharmacology of UGT1A1 substrates, with a special focus on the novel histone deacetylase inhibitor belinostat. Belinostat, approved for the treatment of peripheral T-cell lymphoma, is primarily glucuronidated by UGT1A1. Recent preclinical and clinical data showed that *UGT1A1*28* was associated with reduced glucuronidation in human liver microsomes, while in a retrospective analysis of a Phase I trial with patients receiving belinostat *UGT1A1*60* was predominantly associated with increased belinostat plasma concentrations. Furthermore, both *UGT1A1*28* and **60* variants were associated with increased incidence of thrombocytopenia and neutropenia. Using population pharmacokinetic analysis a 33% dose reduction has been proposed for patients carrying *UGT1A1* variant alleles. Clinical effects of this genotype-based dosing recommendation is currently prospectively being investigated. Overall, the data suggest that *UGT1A1* genotyping is useful for improving belinostat therapy.

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Contents

1. Introduction

In the present era of precision medicine the role of pharmacogenomics has become increasingly important in regards to various aspects of cancer treatment. Pharmacogenomic analyses can be used to predict drug responsiveness in the presence of certain mutations in tumor cells. For example, in the treatment of ovarian cancer progression-free survival is significantly longer in olaparib-treated patients with BRCA mutations than in patients without these mutations [1]. Similarly, patients with non-small cell lung cancer carrying driver mutations in the epidermal growth factor (EGFR) gene benefit more from treatment with EGFR tyrosine kinase inhibitors (e.g., erlotinib [2,3], gefitinib [4], afatinib [5]) than patients with wild type (WT) EGFR. Another example includes the EGFR monoclonal antibodies panitumumab and cetixumab, which appear to be less effective in tumors with KRAS mutations and are therefore recommended only in KRAS WT tumors [6].

Besides having value in predicting drug responsiveness, pharmacogenomics can also be useful in decreasing the incidence of

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Table 1
Common *UGT1A1* variants associated with reduced activity or expression.

UGT1A1 variant	RS number	Variant allele	Variant allele frequency	Effect on UGT1A1
***6**	rs4148323	A	0.13–0.23 (Asians) [22] 0 (Caucasians, Africans) [31]	Reduced activity
***28**	rs8175347	$(TA)_7$	0.26–0.39 (Caucasians) [25,26] 0.30–0.56 (Africans, African Americans) [25,26] 0.09–0.20 (Asians) [25,26]	Reduced expression
***60**	rs4124874	G	0.47 (Caucasians) [29] 0.85 (African Americans) [29]	Reduced expression
***93**	rs10929302	A	0.31 (Caucasians) [29] 0.29 (African Americans) [29]	Reduced expression

adverse drug reactions. For example, the risk of neutropenia in irinotecan-treated patients is higher among patients homozygous for a genetic variant of UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1*28) [7], which is the main metabolizing enzyme of irinotecan's active metabolite SN-38. Furthermore, patients who are deficient in dihydropyrimidine dehydrogenase, the rate limiting enzyme in 5-fluorouracil (5-FU) metabolism, should not undergo treatment with the 5-FU prodrugs fluorouracil [8], capecitabine [9], and tegafur [10] to decrease the risk of drug-related toxicities.

Recent studies suggest that the histone deacetylase (HDAC) inhibitor belinostat (Beleodaq) is another drug for which genotype-directed dosing could be useful to improve drug safety [11–13]. In 2014 belinostat was approved for the treatment of peripheral T-cell lymphoma. Belinostat inhibits the process of histone deactylation by HDAC, which is one of the epigenetic mechanisms that regulate gene expression. HDAC inhibition leads to accumulation of acetylated histones resulting in a more relaxed chromatin structure which enhances the transcription of genes responsible for cell growth arrest, differentiation, and apoptosis of tumor cells [14].

Since belinostat is mainly metabolized by the highly polymorphic enzyme UGT1A1, patients carrying *UGT1A1* variants associated with reduced enzyme function or expression could be exposed to higher belinostat plasma concentrations possibly leading to an increased incidence of belinostat-related toxicities. In this review we therefore evaluate the importance of *UGT1A1* genotyping for belinostat dosing with regards to pharmacokinetics, pharmacodynamics, and toxicities. In addition, clinical effects of *UGT1A1* polymorphisms on the pharmacology of other UGT1A1 substrates (and inhibitors) will be covered.

2. *UGT1A1* polymorphisms

The UGT superfamily consists of four families: UGT1A, UGT2, UGT3, and UGT8 [15]. UGT enzymes are responsible for glucuronidation of endogenous (e.g., bilirubin) or drug substrates thereby increasing water solubility and biliary or renal clearance of these compounds.

UGT1A1, located on chromosome 2q37, is expressed in the stomach [16], liver, colon, and intestine [17]. The main function of hepatic UGT1A1 is glucuronidation of bilirubin [18]. Consequently, UGT1A1-deficiencies lead to hyperbilirubinemia as observed in patients with Crigler–Najjar syndrome [19] and Gilbert's syndrome [20]. Thus far, 113 *UGT1A1* genetic variants have been described [21], of which *UGT1A1*6* (rs4148323), *UGT1A1*28* (rs8175347), *UGT1A1*60* (rs4124874), and *UGT1A1*93* (rs10929302) are commonly reported variants associated with reduced enzyme expression or activity (Table 1).

*UGT1A1*6*, a glycine-to-arginine substitution at position 71, has an allele frequency of 0.13–0.23 in Asians [22]. Individuals homozygous for *UGT1A1*6* have their UGT1A1 activity reduced by ~70%, which may contribute to the development of Gilbert's syndrome [23] and nonphysiologic neonatal hyperbilirubinemia [24].

*UGT1A1*28* is characterized by an extra TA repeat ($A(TA)_7TAA$) in the *UGT1A1* promoter region [20]. This genetic variant reduces UGT1A1 expression by approximately 70% compared to WT $A(TA)_6TAA$ and is associated with Gilbert's syndrome [20]. Reported allele frequencies are 0.26–0.39 in Caucasians, 0.30–0.56 in Africans and African Americans, and 0.09–0.20 in Asian populations [25,26].

Besides the polymorphic $(TA)_n$ repeat, the phenobarbital-responsive enhance module (PBREM) also regulates *UGT1A1* transcription and harvests genetic variation [27]. For example, *UGT1A1*60*, caused by a T-to-G substitution at position 3279, decreases the transcriptional activity of the *UGT1A1* gene [28]. Allele frequencies of *UGT1A1*60* in Caucasians and African Americans are 0.47 and 0.85, respectively [29]. This variant is in linkage disequilibrium with *UGT1A1*28* [29].

*UGT1A1*93* is a G-to-A substitution at position 3156 in the PBREM and also in linkage disequilibrium with *UGT1A1*28* [29]. Individuals homozygous for *UGT1A1*93* had higher total bilirubin concentrations than WT *UGT1A1*93* [30]. Frequency of the variant allele is approximately 0.30 in Caucasians and African Americans [29].

3. Effects of *UGT1A1* polymorphisms on belinostat pharmacokinetics, pharmacodynamics, and toxicities

3.1. Clinical pharmacology of belinostat

The recommended dosage of belinostat is 1000 mg/m^2 administered intravenously (IV) over 30 min once daily on days 1–5 of a 21-day cycle [32]. Nausea, fatigue, pyrexia, anemia, and vomiting are the most common toxicities [32]. After administration belinostat is limitedly distributed to tissue (as indicated by a mean volume of distribution approaching total body water) and shows extensive protein binding of 93–96%.

Using a panel of human UGT supersomes, each specifically expressing UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15 or UGT2B17, Wang and colleagues have shown that belinostat was metabolized only by UGT1A1 [11]. The vast majority (98%) of belinostat undergoes hepatic metabolism, primarily by UGT1A1 and to a lesser extent by CYP2A6, CYP2C9, and CYP3A4. Less than 2% of belinostat is excreted unchanged in urine. Elimination of belinostat is rapid with an elimination half-life of only 1.1 h [32].

3.2. *Effects of* UGT1A1 *genotyping on the clinical pharmacology of belinostat*

Studies of UGT1A1-mediated metabolism of belinostat identified five metabolites in plasma samples of patients treated with belinostat [11]. Of these metabolites, belinostat glucuronide (belinostat-G) was found to be the most abundant one, suggesting that glucuronidation is the main metabolic pathway of belinostat. In HepG2 cells belinostat was shown to be cytotoxic, while belinostat-G was inactive. After the discovery that UGT1A1