

## Complications of Treatment

## The role of drug–drug interactions in prostate cancer treatment: Focus on abiraterone acetate/prednisone and enzalutamide



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## ABSTRACT

Elderly patients with cancer may have comorbidities, each requiring additional pharmacologic treatment. Therefore, the occurrence of pharmacokinetic (PK) and pharmacodynamic (PD) interactions is very likely, and the risk of adverse reactions (ADRs), due to the narrow therapeutic window of anticancer drugs, is increased. Drug–drug interactions (DDIs) may occur in prostate cancer patients due to inhibition by abiraterone of liver cytochrome P450 (CYP)-dependent enzymes CYP2C8 and 2D6, which are involved in the metabolism of approximately 25% of all drugs, and induction by enzalutamide of CYP3A4, 2C9 and 2C19, which metabolize up to 50% of medications. Therefore, abiraterone may increase plasma levels of CYP2D6 substrates, including amitriptyline, oxycodone and risperidone, as well as of CYP2C8 substrates including amiodarone and carbamazepine. Since enzalutamide is extensively metabolized by CYP2C8, its plasma levels are likely to be raised if coadministered with strong CYP2C8 inhibitors such as gemfibrozil or pioglitazone. Inducers of CYP2C8 (i.e., rifampin) may reduce the effectiveness of enzalutamide and hence should be avoided. Enzalutamide may decrease plasma levels of CYP3A4, 2C9 and 2C19 substrates including disopiramide, quetiapine, quinidine and warfarin. Growing awareness of the importance of DDIs in cancer patients is now reflected in the variety of web-based sources offering information and guidance. However, the evaluation of the clinical relevance of DDIs is the result of a comprehensive evaluation of many factors, including therapeutic index, amplitude of therapeutic range and presence of comorbidities, requiring a specific expertise in clinical pharmacology.

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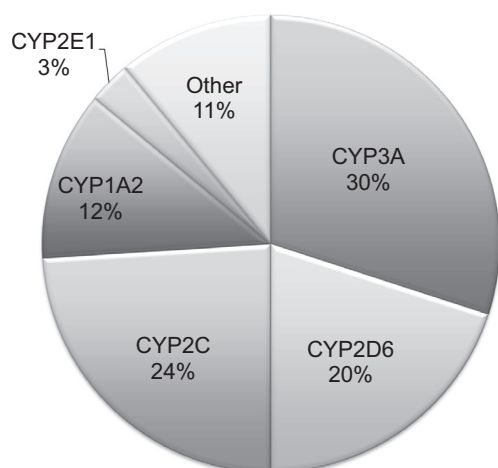
## Introduction

The main liver enzymes involved in drug metabolism belong to the cytochrome P450 (CYP450) family, and are housed in the smooth endoplasmic reticulum of the cell [1]. Metabolism is divided into phase I and phase II [2,3]; some drugs may undergo only phase I or phase II metabolism, but, more often, medications are subjected to phase I and II, sequentially. Phase I metabolism involves reduction or hydrolysis of the drug, but the most common biochemical process is oxidation by CYP450 enzymes, which

results in the loss of electrons from the substrate [4]. The drug is now said to be oxidized and, after phase I reactions, the resulting metabolite is often pharmacologically active. The CYP450 enzymes are grouped in subfamilies such as CYP2C or 3A, and the individual enzymes are numbered as CYP2C8 or 3A4. CYP3A4 is responsible for the oxidation of unrelated drugs such as dapson (N-hydroxylation), diazepam (3-hydroxylation), taxol (3'-hydroxylation) and warfarin ((S)-4'-hydroxylation) [5]. CYP3A4 metabolizes almost 30% of all drugs administered to humans, while CYP2D6 and 2C9 metabolize 20% and 12.8% of all medications, respectively [3,6] (Fig. 1). CYP2D6 metabolizes by oxidation alprenolol, amiodarone (aromatic hydroxylation), debrisoquine (4-hydroxylation), imipramine (2-hydroxylation), propranolol (4-hydroxylation), codeine (O-demethylation) and others [7].

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**Fig. 1.** Proportion of drugs metabolized by the major cytochrome P450 (CYP) isozymes.

CYP2C9 oxidizes ibuprofen, phenytoin, tenoxicam, tolbutamide and warfarin [8].

Factors affecting liver metabolism, including ageing and viral diseases, or conditions that reduce hepatic blood flow, i.e., cardiac insufficiency, may also impair the metabolic activity of the liver. Metabolism can also be altered due to genetic variants of selected enzymes; indeed, CYP450 family is highly polymorphic [9,10] and individuals can be stratified as poor, intermediate, rapid and ultrarapid metabolizers based on their phenotype [10,11]. The coadministration of drugs as well as dietary and environmental factors can influence liver metabolic function. For example, grapefruit juice inhibits CYP3A4 activity in the gut [12], while cigarette smoke and St John's wort induce CYP450 activity [13,14].

Criteria to define the level of interaction are based on phenotypic changes [15]; as an example, strong, moderate, and weak inhibitors are drugs that increase the area under the plasma concentration–time curve (AUC) of sensitive index substrates of a given metabolic pathway  $\geq 5$ -fold,  $\geq 2$  to  $< 5$ -fold, and  $\geq 1.25$  to  $< 2$ -fold, respectively [16]. Strong, moderate, and weak inducers are drugs that decrease the AUC of sensitive index substrates of a given metabolic pathway by  $\geq 80\%$ ,  $\geq 50\%$  to  $< 80\%$ , and  $\geq 20\%$  to  $< 50\%$ , respectively [16].

### Enzyme induction and inhibition

Each CYP isoform possesses a characteristic spectrum of catalytic activities on substrates. The ability of a single CYP to metabolize multiple drugs is the reason for the large number of drug-drug interactions (DDIs) associated with CYP induction or inhibition. DDIs can occur as the result of the induction of human CYPs following long term drug treatment [17]. Enzyme induction occurs at nuclear level and is the result of xenobiotic-induced increase in transcriptional activity of a gene, which can be of long duration [17,18]. It usually occurs after repeated administrations of a drug and persists for additional time after treatment interruption, owing to the formation of new enzyme molecules. On the contrary, CYP inhibition occurs rapidly after the start of treatment [19] and usually enzyme activity recovers within a short period of time. The mechanisms of CYP inhibition [20] can be divided into 3 categories: (a) reversible inhibition; (b) *quasi*-irreversible inhibition; and (c) irreversible inhibition [21,22]. In mechanistic terms, reversible interactions are the result of substrate competition at the CYP active site and probably involve only the first step of the CYP catalytic cycle [21,22]. On the other hand, drugs acting during and

**Table 1**

Factors affecting the clinical relevance of DDIs and their management by clinical observation or TDM.

Characteristics to be considered	Consequences
Therapeutic index of the drug Therapeutic window of drug concentrations	Little deviations from therapeutic concentrations are associated with the risk of ADRs if drugs have a low therapeutic index or narrow window of plasma levels
Co-morbidities (i.e., liver and renal dysfunction, hypoproteinemia)	Inhibition of liver or renal CL or plasma protein displacement by interfering drugs may be associated with higher susceptibility to ADRs
Single vs. multiple metabolic pathways	Alternative metabolic pathways may compensate in case of inhibition of a prevalent pathway
Availability of drug assay platform	TDM may be useful to demonstrate significant changes in drug levels and may help dose adjustment

after the oxygen transfer step are generally irreversible or *quasi*-irreversible inhibitors and in this case enzyme inhibition requires at least one cycle of the CYP catalytic process [22].

Because human liver samples and recombinant human CYPs are now available, *in vitro* systems have been used as screening tools to predict the potential for *in vivo* DDIs [23]. Although it is easy to determine *in vitro* metabolic DDIs, the proper interpretation and extrapolation of *in vitro* interaction data to the *in vivo* setting require in-depth understanding of PK principles. In real-life, DDIs by mutual interaction between drugs are very frequent, because CYP-mediated metabolism represents a major route of elimination of most drugs, which may compete for the same CYP [22]. The clinical significance of a metabolic DDI depends on the magnitude of the change in the concentration of active moieties (parent drug and/or active metabolites) at the site of pharmacological action and the therapeutic index of the drug (Table 1). The smaller the difference between toxic and effective concentration, the greater the likelihood that a DDI will have serious clinical consequences. Also, genetic variants of CYPs have a rather large impact on enzyme activity and may significantly change the susceptibility to DDIs [24]. Thus, careful evaluation of potential DDIs of a new drug candidate during the early stage of drug development is crucial [22,25].

### Overview of DDIs

DDIs may be defined as a clinical or pharmacological event due to the co-exposure of a drug with another drug that can modify the patient's response to therapy [26]. Food and herbal medicines may also significantly affect drug absorption and metabolism and represent an important cause of drug interaction [27]. The result of this process includes a variety of PK or PD mechanisms that can have different outcomes: decreasing or increasing the efficacy of treatment (i.e., PK enhancers in HIV treatment [28]) and inducing adverse drug reactions (ADRs) [29]. In clinical practice, little is known about DDIs and the management of patients, especially if they are elderly and with cancer. Indeed, the consequences of DDIs generally depend on the status of patients (age, comorbidities, hepatic and renal function), the presence of genetic polymorphisms that influences the individual responses and the administered drug as well [30]. The use of multiple medications by a patient is a recognized independent risk factor for serious ADRs and increases the risk of hospitalization and mortality, especially in the elderly population where the prevalence of polypharmacy ranges from 13% to 92% [31]. In oncology, elderly subjects with cancer are a risk group and prostate cancer patients are also at high risk to be exposed to potentially harmful DDIs because they receive multiple

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