Label differences for anticancer drugs with pharmacogenomic associations

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Introduction

Pharmacogenomics (PGx) uses genetic information to personalise drug therapy, application of which may increase medication efficacy and reduce the risk of adverse drug reactions (ADRs). This is particularly relevant in oncology because of the risk of reduced efficacy or serious toxicity[1]. Information on anticancer drug labels provides an incentive for clinical implementation of PGx. Any information included in the label is driven by the strength of evidence and by its clinical utility, defined as the ability to inform clinical decision making and thereby improve the benefit-risk balance with use of the drug. However, significant differences in regulatory approved labelling regarding PGx have been observed[2].

Objectives

To review important discrepancies in anticancer drug labels regarding PGx information.

Methods

Drug labels for oncology medicines with known PGx associations from different regulatory authorities were compared. Those with major differences in labelling information were selected for further review.

Results

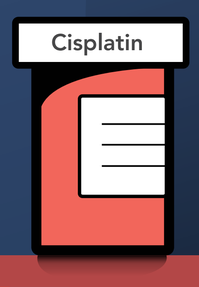
Examples of differences in PGx information on drug labels for oncology medicines are shown in the tables below.

Conclusions

Discrepancies in anticancer drug labels regarding PGx information were identified between three regulatory bodies, which may be caused by the differences in understanding of what is clinically useful information. This reinforces the need for critical evaluation and possible harmonisation of PGx labels between countries.

EU[6]	USA[7]	CANADA[8]
Section 4.4 Special warnings and precautions for use: Concomitant medications that inhibit CYP2D6 may lead to reduced concentrations of the active metabolite endoxifen. Therefore, potent inhibitors of CYP2D6 (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should whenever possible be avoided during tamoxifen treatment. **Section 5.1 Pharmacodynamic properties** *CYP2D6* genotype Available clinical data suggest that patients, who are homozygote for non-functional *CYP2D6* alleles, may experience reduced effect of tamoxifen in the treatment of breast cancer. The available studies have mainly been performed in postmenopausal women (see sections 4.4 and 5.2)	**Section 7 Drug interactions – Strong Inhibitors of CYP2D6** The impact on the efficacy of tamoxifen with co-administration of strong CYP2D6 inhibitors (e.g. paroxetine) is not well established. Some studies have shown that the efficacy of tamoxifen may be reduced when the drugs are co-administered as a result of reduced levels of potent active metabolites of tamoxifen. However, other studies have failed to demonstrate such an effect. **Section 12 Clinical Pharmacology – Pharmacogenomics** The impact of *CYP2D6* polymorphisms on the efficacy of tamoxifen is not well established. *CYP2D6* poor metabolizers carrying two non-functional alleles exhibit significantly lower endoxifen plasma concentrations compared to patients carrying one or more fully functional alleles of *CYP2D6*.	**Warnings** Low CYP2D6 activity that occurs in patients harbouring certain *CYP2D6* alleles (i.e. *4) or from the chronic use of CYP2D6 inhibitors can lead to persistent reductions in plasma concentrations of an active metabolite of tamoxifen citrate (endoxifen). Reduced efficacy on tamoxifen citrate has been reported with concomitant usage of some selective serotonin reuptake inhibitor (SSRI) antidepressants (e.g. paroxetine, a known CYP2D6 inhibitor). Concurrent chronic use of CYP2D6 inhibitors that may affect tamoxifen citrate efficacy should be avoided if possible.

Table 2. Differences in drug labels regarding PGx information for tamoxifen and CYP2D6



EU[3]	USA[4]	CANADA
No information.	**Section 5.6 Warnings and precautions – Ototoxicity** Genetic factors (e.g. variants in the thiopurine S-methyltransferase [TPMT] gene) may also contribute to cisplatin-induced ototoxicity; although this association has not been consistent across populations and study designs.	No information.* *Guidelines by the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) clinical recommendation group recommend testing for the TPMT alleles *2, *3A, *3B or *3C in all pediatric cancer patients due to the association of these alleles with an increased risk of cisplatin-induced ototoxicity[5].

Table 1. Differences in drug labels regarding PGx information for cisplatin and TPMT

References/further sources of information

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