IRISH MEDICINES BOARD

Tamoxifen – Risk of Reduced Therapeutic Response

Tamoxifen is a selective oestrogen receptor modulator indicated for palliative and adjuvant treatment of oestrogen receptor positive breast cancer in pre- and post-menopausal women.

Tamoxifen undergoes extensive metabolism to form metabolites, which have similar or enhanced pharmacological activity compared with tamoxifen and contribute to the therapeutic effect. The formation of active metabolites (e.g. endoxifen) is predominantly mediated by the cytochrome P450 CYP2D6 enzyme.

Recently, a number of studies have examined the potential effect of CYP2D6 genetic variants on clinical response to tamoxifen treatment. The studies gave rise to the concern that patients with inherited non-functional alleles of the gene coding for CYP2D6 or patients who are concomitantly treated with medicines inhibiting CYP2D6, might not be suitable for adjuvant tamoxifen therapy, due to reduced concentrations of those metabolites of tamoxifen that bind most strongly with the oestrogen receptor expressed by the breast cancer.

The Pharmacovigilance Working Party (PhVWP) of the European Medicines Agency conducted a review of the available evidence in this respect. The review included all currently available data and the limitations and interpretation of the published studies. Further information on the review and references are included in the PhVWP report available from http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500097444.pdf.

Outcome of review

Based on the totality of evidence, the PhVWP considered that the available published data, mainly on post-menopausal women treated for breast cancer with tamoxifen, suggest that CYP2D6 polymorphism status may be associated with different therapeutic response of patients to tamoxifen. Poor CYP2D6 metaboliser status may be associated with reduced response. The consequences of the findings for the treatment of poor CYP2D6 metabolisers have not been fully understood. The available data at present have not clearly shown the clinical utility of CYP2D6 testing to predict tamoxifen efficacy and clinical outcome. There is insufficient evidence at present to recommend genotyping patients before starting tamoxifen treatment.

Additionally, the PhVWP noted that pharmacokinetic interactions with CYP2D6 inhibitors were described in the medical literature, showing a 65-75% reduction in plasma levels of one of the more active forms of tamoxifen, i.e. endoxifen. Reduced efficacy of tamoxifen was reported with concomitant use of some SSRI antidepressants (e.g. paroxetine). However, in other studies, a decrease in efficacy of tamoxifen with co-administration of CYP2D6 inhibitors was not evident. As a reduced effect of tamoxifen cannot be excluded, particularly in the context of the pharmacokinetic data and mechanistic plausibility, co-administration with potent CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should be avoided whenever possible.

The product information for medicinal products containing tamoxifen will be updated to highlight the possible reduction in therapeutic response to tamoxifen in poor CYP2D6 metabolisers and to warn against using potent CYP2D6 inhibitors during tamoxifen treatment whenever possible.

Key message:

Avoid use of potent CYP2D6 inhibitors during tamoxifen treatment whenever possible and be aware that poor CYP2D6 metabolisers may respond less well to tamoxifen treatment.

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