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Genetic testing to inform tamoxifen prescribing

Bulletin for Prescribers | June 2020

Analysis of the CYP2D6 gene identifies patients who will benefit from modified tamoxifen prescribing.

Approximately 70% of breast cancers are hormone-sensitive, expressing oestrogen or progesterone receptors. In this group of patients, hormone therapy is a long-established form of treatment. Tamoxifen is a selective oestrogen receptor modulator that has been a mainstay of hormone therapy for decades. It has a proven role in the prevention and treatment of pre- and post-menopausal breast cancer.

The metabolism of tamoxifen

The metabolism of tamoxifen is complex.[1] Tamoxifen is a weak anti-oestrogen. It is converted by the cytochrome P450 enzymes CYP3A4 and CYP2D6 to endoxifen, which has 100-fold more anti-oestrogen activity than the parent drug.

The clinical effectiveness of tamoxifen is tied to the activity of the CYP2D6 enzyme. Patients who have low CYP2D6 activity ('poor metabolisers') convert less of the parent tamoxifen to endoxifen, and have higher risks of breast cancer recurrence than those with normal CYP2D6 activity ('normal metabolisers'). Low CYP2D6 activity is caused by inherited variants in the CYP2D6 gene that make poor or non-functional CYP2D6 enzyme, and by medications that inhibit enzyme activity directly.

Genetic testing to identify poor metabolisers

The CYP2D6 gene is highly variable, with many different variants identified at different frequencies in various populations globally.[2] These variants can diminish or increase the activity of the enzyme encoded by the gene. Patients can be categorised according to the level of CYP2D6 enzyme activity, with a range of frequencies observed in different ethnic groups.

Metaboliser status of patient	Frequency
Poor metaboliser	0.4–5%
Intermediate metaboliser	0.4–11%
Normal metaboliser	67–90%
Ultrarapid metaboliser	1–21%

The Sonic PGx Panel includes analysis of the CYP2D6 gene and reports CYP2D6 metaboliser status. Metaboliser status cannot be predicted on the basis of ethnicity, gender, age or cancer diagnosis.

Clinical significance of CYP2D6 metaboliser status

There is unequivocal evidence that metaboliser status is a key determinant of endoxifen concentration in serum, and that endoxifen concentration is inversely associated with risk of breast cancer relapse or death.[1] These observations were reflected in the outcomes of a major clinical trial in which poor metabolisers exhibited increased risk of distant recurrence and all-cause mortality at nine years.[3]

Other clinical trials evaluating CYP2D6 metaboliser status and benefit from tamoxifen have yielded conflicting results.[4] The marked heterogeneity across different trials can be attributed to variations in the dose and duration of tamoxifen therapy and in the performance of the genetic tests used. For example, some studies had analysed tumour tissue and were compromised by the frequent chromosome deletions and duplications which can occur in cancer cells. The prediction of a patient's metaboliser status should only be done on analysis of normal tissue, for example, blood or buccal cells.

T Sonic Genetics 1800 010 447 · **E** info@sonicgenetics.com.au · **www.sonicgenetics.com.au**

Prescribing recommendations

Guidance regarding the use of CYP2D6 metaboliser status to inform tamoxifen prescribing has been developed by a number of expert bodies, including the Clinical Pharmacogenetics Implementation Consortium,[1] the Dutch Pharmacogenetics Working Group,[5] and the Canadian Pharmacogenomics Network for Drug Safety.[6]

The Sonic PGx Panel report provides specific guidance for prescribing tamoxifen on the basis of the patient's CYP2D6 metaboliser status and these international guidelines. In brief, there is a strong recommendation that patients identified as poor CYP2D6 metabolisers should avoid tamoxifen and take an aromatase inhibitor (which is not metabolised by CYP2D6).[1] For intermediate CYP2D6 metabolisers, either an aromatase inhibitor or an increased dose of tamoxifen may be considered. Patients who are normal or ultrarapid metabolisers should be prescribed the usual dose of tamoxifen.

Medications that inhibit the CYP2D6 enzyme

In addition to low CYP2D6 activity due to variants in the CYP2D6 gene, numerous medications can directly inhibit the CYP2D6 enzyme to varying degrees. Patients taking tamoxifen should probably avoid these medications, especially those patients who are not normal or ultrarapid CYP2D6 metabolisers. Some common inhibitors of CYP2D6 are mentioned below, but this is not a complete list.

Antidepressants are an important consideration. Fluoxetine, paroxetine, bupropion, duloxetine and moclobemide are strong to moderate inhibitors of CYP2D6 and probably reduce tamoxifen effectiveness. Other antidepressants, such as citalopram, escitalopram, venlafaxine, desvenlafaxine, fluvoxamine, sertraline and the tricyclic antidepressants, including amitriptyline and doxepin, are weak inhibitors of CYP2D6. Their effects may still be relevant in patients who are intermediate CYP2D6 metabolisers, because this combined genetic and drug interaction may also significantly reduce endoxifen concentrations. Weak inhibitors of CYP2D6 are of less clinical concern in breast cancer patients who are normal or ultrarapid metabolisers of tamoxifen.

The Sonic PGx Panel is available nationally through Sonic Genetics. The cost is $197^ and a Medicare rebate is not available. The turnaround time is up to 7 business days, and results can be accessed electronically via Sonic Dx, by fax, or by phone.

For further information, visit the Sonic Genetics website, www.sonicgenetics.com.au/pgx. Please contact us on 1800 010 447 or email info@sonicgenetics.com.au should you have any enquiries.

^Correct at time of printing

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