White Paper

Therapeutic Drug Monitoring of Tamoxifen

Clinical use

- Determine patient adherence with tamoxifen therapy
- Determine adequacy of tamoxifen therapy in women with breast cancer

Clinical Background

Tamoxifen is widely prescribed for women with early-stage estrogen receptor positive (ER+), HER2-negative breast cancer. After finishing their treatment for the cancer, they are prescribed tamoxifen to prevent relapse. A 5- to 10-year treatment delays local and distant recurrence, prolongs overall survival, and reduces the incidence of contralateral breast cancer.

Since tamoxifen is a prodrug, it must be metabolized in the body to be active; the primary active metabolites are endoxifen and 4-hydroxy tamoxifen. Compared with tamoxifen, these two metabolites have a 100-fold greater affinity for ER and a 30- to 100-fold greater potency in suppressing estrogen-dependent cell proliferation. Endoxifen is the more important, with levels being 5-10 times higher than that of 4-hydroxy tamoxifen.

Endoxifen concentration is impacted by tamoxifen metabolism, which in turn is affected by liver disease, certain drugs, and polymorphisms in the cytochrome P450 *CYP2D6* gene. *CYP2D6* polymorphisms confer differential metabolism and may result in endoxifen concentrations that are significantly different in *CYP2D6* extensive metabolizers as compared to poor metabolizers. Although genetic testing for *CYP2D6* polymorphisms is available, a person's *CYP2D6* genotype does not fully predict endoxifen levels or the outcome of tamoxifen therapy (7).

The effect of endoxifen appears to be concentration dependent; low concentrations are associated with a worse prognosis including a greater risk of recurrence and mortality. For patients with endoxifen concentrations below the predefined threshold, an increase of the tamoxifen dose reduce the risk for relapse. Increasing the tamoxifen dose leads to a significantly higher serum concentration of tamoxifen and its metabolites (1, 2, 3, 4).

A very important factor is the adherence to therapy, which may be as low as 50%. Poor adherence and early discontinuation are both associated with an increased risk of breast cancer events (5). Both poor and ultra-rapid *CYP2D6* metabolizers of tamoxifen have a worse prognosis for breast cancer compared with normal, intermediate metabolizers.

Ultra-rapid metabolizers that take the standard dose of tamoxifen, 20 mg/day, can have an endoxifen level more than twice the accepted therapeutic level. They are also significantly more likely to use symptom relieving drugs and discontinue tamoxifen use. Studies have hypothesized that the concentration of endoxifen should be within a certain therapeutic range to balance tamoxifen efficacy and adverse drug reactions. Exceeding this range may have negative therapeutic effects, leading to live threatening or intolerable adverse effects (4, 5). Biomarker studies have also suggested that there may be a case for reducing the current standard dose of tamoxifen, especially for ultra and extensive metabolizers, to reduce side effects while maintaining efficacy (6).

That poor metabolizers might be at risk when using standard treatment (20 mg/day), was highlighted in a study on 1 370 patients (7), which showed that the concentrations of endoxifen and 4-hydroxy tamoxifen was strongly associated with the *CYP2D6* phenotype. A risk group was identified with endoxifen levels below the predefined threshold. Importantly, however, while the majority (76%) in this group were poor metabolizers, 24% of them may be able to obtain therapeutic levels of endoxifen despite their poor metabolizer status. Metabolizer phenotype alone may not be enough to determine whether tamoxifen is of potential benefit to any individual patient. In the same study, participants with endoxifen concentrations above the threshold had a 30% lower risk of additional breast cancer events (7).

Therapeutic drug monitoring based on tamoxifen metabolite concentrations take into account the factors that impact tamoxifen effectiveness, including inter-individual variation caused by *CYP2D6* polymorphisms, liver disease, drugs, and patient adherence. It is a direct measure of the amount of active drug in the individual patient. Furthermore, studies have shown a correlation between endoxifen levels and outcomes of tamoxifen therapy. Patients without side effects should be therapeutic drug monitored to exclude the risk of poor bioactivation of tamoxifen (8). Tamoxifen dose adjustment, in combination with concentration monitoring of tamoxifen metabolites, will maximize tamoxifen efficacy while maintaining patients' quality of life and adherence to therapy (8).

Taken together, this literature survey suggests that monitoring of tamoxifen and its metabolites in the blood, seems to be a more effective way to determine the adequacy of tamoxifen treatment rather than *CYP2D6* genotyping. Therapeutic drug monitoring for optimizing and personalizing tamoxifen treatment of breast cancer patients is therefore of significant importance, as well as the adherence to therapy.

Individuals Suitable for Testing

Women with breast cancer who are receiving tamoxifen therapy

Method

Liquid Chromatography, tandem mass spectrometry (LC-MS/MS-MS/MS)

	Reference Range	**Limit of Quantitation**
Tamoxifen	1.0 – 200.0 ng/mL	1 ng/mL
Endoxifen	0.20 – 200.0 ng/mL	0.2 ng/mL
4OH Tamoxifen	0.20 – 200 ng/mL	0.2 ng/mL

Interpretive Information

Clinical cutoffs for tamoxifen and its metabolites are not yet fully established. However, compiled data from a number of publications indicate a preferred therapeutic concentration window for endoxifen and 4-OH tamoxifen.

- An investigation of 1 370 patients showed that a risk group could be identified with endoxifen levels < 5.9 ng/mL (7).
- In patients that took 20 mg tamoxifen/day a study on 91 clinical samples the tamoxifen, endoxifen and 4-hydroxy tamoxifen levels was 123.2 ng/mL, 9.1 ng/mL respectively 1.4 ng/mL (9).
- Three studies where patients were using 20 mg tamoxifen per day report mean endoxifen concentrations between 7.10 and 14.5 ng/mL and mean 4-OH tamoxifen levels between 1.55 and 2.25 ng/mL (10,11,12) whereas another study on 75 patients reports concentrations twice as high (13). However, after comparative analysis with a more specific LC_MS/MS method, the re-analyzed samples showed concentrations in line with the ones obtained in refs 10-12; endoxifen 9 ng/mL and 4-OH tamoxifen 1.7 ng/mL (14).
- Three studies investigating the association between *CYPCD2* genotypes and serum concentrations show corroborating endoxifen results for the phenotype groups; ultra-rapid (10-16 ng/ml), extensive (7.5-12 ng/ml), intermediate (3.5-9 g/ml) and poor metabolizers (1.5-4.5 ng/ml) (3, 8, 16).
- A study including 99 patients showed that patients with endoxifen concentrations > 3.35 ng/mL and 4-hydroxy tamoxifen concentrations > 1.26 ng/mL had a survival rate of > 80%, as compared to < 60% for patients with lower concentrations (15).
- Patients with endoxifen concentrations >10.2 ng/mL, i.e. corresponding to strata 3–4 in the Madlensky study (7) and 29% of the study population in ref. 8, had significantly more severe side effects than patients with lower endoxifen levels. These findings are in line with an investigation where dose reduction of tamoxifen from 20 to 10 mg daily with a corresponding drop in endoxifen plasma levels from approximately 10 to 5 ng/mL, was associated with less problems of hot flushes (17).

CONCLUSION

A preferred therapeutic concentration of endoxifen should be in the range of 6.0 to 15.0 ng/mL and the 4-hydroxy tamoxifen concentration should be in the range of 1.0 to 2.0 ng/mL.

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