Safety Alert

Potential for Significant Drug Interaction:

Tamoxifen & SSRI/SNRI Antidepressants

Issue

- Tamoxifen is a selective oestrogen receptor modulator widely prescribed to treat hormone receptor positive breast cancer. It has been shown to reduce annual breast cancer mortality rate by one third and the 5-year recurrence rate by 50%.[1,2]
- Tamoxifen is a prodrug that is extensively metabolised via Cytochrome P450 (CYP2D6) isoenzymes in the liver to active metabolites the most significant of which is **endoxifen**.[1,2,3]
- Nearly half of women with breast cancer report depression, anxiety or both.[2]
- The selective serotonin reuptake inhibitor (SSRI) paroxetine is a potent CYP2D6 inhibitor, fluoxetine is a moderate to potent inhibitor, and duloxetine, a selective noradnenaline reuptake inhibitor (SNRI), is a moderate CYP2D6 inhibitor.[1]
- Pharmacokinetic studies have shown that Endoxifen levels can be up to 66% lower in patients treated with tamoxifen and concomitant paroxetine or fluoxetine, than in patients treated with tamoxifen alone.[1]
- While most sources classify sertraline as a weak inhibitor of CYP2D6, the enzyme-inhibiting effect is dose-related. Clinicians should consider the potential for sertraline to reduce tamoxifen/endoxifen concentrations at doses ≥150mg/day.[5]

Evidence of Harm

- A population based cohort study assessing SSRI antidepressants and breast cancer mortality in women receiving tamoxifen found that the risk of death from breast cancer increased with the length of concomitant treatment with paroxetine a potent inhibitor of CYP2D6, but not with other SSRIs.[3,7]
- A more recent (2016) large population based study found no evidence for decreased efficacy with the co-administration of fluoxetine/paroxetine and tamoxifen.[2]
- Overall, pharmacoepidemiological data for the drug interaction between tamoxifen and SSRIs/SNRIs are conflicting and inconclusive. Follow-up is often too brief to establish survival differences. However, given the biologically plausible mechanism of enzyme inhibition, the potential consequences of failed tamoxifen therapy and the delayed manifestation of these consequences, the manufacturer and MHRA (UK) continue to recommend that people who are prescribed tamoxifen should not be prescribed potent or moderately potent CYP2D6 inhibitors.

How to Reduce the Risks

- Concomitant use of drugs that are potent or moderately potent inhibitors of the CYP2D6 enzyme should be avoided whenever possible in patients treated with tamoxifen for breast cancer.[1,3,4]
- Alternative antidepressants with weak to no effect on CYP2D6 should be considered eg. citalopram, escitalopram, venlafaxine or mirtazapine.[1,3,4,8]

References

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