Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial

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Summary

Background
Vasomotor symptoms and bone loss are complications frequently induced by adjuvant treatment for breast cancer. Tibolone prevents both side-effects, but its effect on cancer recurrence is unknown. The aim of this study was to show non-inferiority of tibolone to placebo regarding risk of recurrence in breast-cancer patients with climacteric complaints.

Methods
Between July 11, 2002, and Dec 20, 2004, women surgically treated for a histologically confirmed breast cancer (T1–3N0–2M0) with vasomotor symptoms were randomly assigned to either tibolone 2·5 mg daily or placebo at 245 centres in 31 countries. Randomisation was done by use of a centralised interactive voice response system, stratified by centre, with a block size of four. The primary endpoint was breast-cancer recurrence, including contralateral breast cancer, and was analysed in the intention-to-treat (ITT) and per-protocol populations; the margin for non-inferiority was set as a hazard ratio of 1·278. This study is registered with ClinicalTrials.gov, number NCT00408863.

Findings
Of the 3148 women randomised, 3098 were included in the ITT analysis (1556 in the tibolone group and 1542 in the placebo group). Mean age at randomisation was 52·7 years (SD 7·3) and mean time since surgery was 2·1 years (SD 1·3). 1792 of 3098 (58%) women were node positive and 2185 of 3098 (71%) were oestrogen-receptor positive. At study entry, 2068 of 3098 (67%) women used tamoxifen and 202 of 3098 (6·5%) women used aromatase inhibitors. The mean daily number of hot flushes was 6·4 (SD 5·1). After a median follow-up of 3·1 years (range 0·01—4·99), 237 of 1556 (15·2%) women on tibolone had a cancer recurrence, compared with 165 of 1542...
(10·7%) on placebo (HR 1·40 [95% CI 1·14–1·70]; p=0·001). Results in the per-protocol population were similar (209 of 1254 [16·7%] women in the tibolone group had a recurrence vs 138 of 1213 [11·4%] women in the placebo group; HR 1·44 [95% CI 1·16–1·79]; p=0·0009). Tibolone was not different from placebo with regard to other safety outcomes, such as mortality (72 patients vs 63 patients, respectively), cardiovascular events (14 vs 10, respectively), or gynaecological cancers (10 vs 10, respectively). Vasomotor symptoms and bone-mineral density improved significantly with tibolone, compared with placebo.

**Interpretation**
Tibolone increases the risk of recurrence in breast cancer patients, while relieving vasomotor symptoms and preventing bone loss.

**Funding**
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