**TRIAL SUMMARY: Ovarian function suppression plus tamoxifen**

Francis PA, Regan MM, Fleming GF. Randomized comparison of adjuvant tamoxifen (T) plus ovarian function suppression (OFS) versus tamoxifen in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC): Analysis of the SOFT trial. 2014 San Antonio Breast Cancer Symposium Abstract S3-08.

The role of the addition of ovarian function suppression (OFS) to endocrine therapy in premenopausal women with early-stage breast cancer is unclear. The SOFT trial compared 5 years of tamoxifen (T) alone to tamoxifen+OFS (T+OFS) or exemestane+OFS (E+OFS). Three thousand and sixty-six premenopausal women were randomized to 5 years of tamoxifen alone vs T+OFS vs E+OFS. OFS was achieved through a gonadotropin-releasing hormone (GnRH) agonist (triptorelin), surgery or radiation. They were stratified according to prior chemotherapy, with 43% having received no chemotherapy and 53% remaining premenopausal after chemotherapy (confirmed with estradiol levels). As expected, those with prior chemotherapy had tumours with more aggressive characteristics (bigger tumour, higher grade, more positive lymph nodes) and were younger. The primary endpoint was DFS with secondary endpoints being breast cancer-free interval (BCFI), distant recurrence-free interval (DRFI) and OS.

**Results:** Median followup was 67 months. There was no significant difference in PFS in the whole group between T alone vs T+OFS (86.6% vs 84.7%; HR=0.83; 95% CI, 0.86–1.04; p=0.10). OS data is still immature and both groups have a 5-year survival of over 95%. However, when the group that had received prior chemotherapy was analyzed separately, there was an absolute difference of 4.5% in BCFI for the T+OFS group and improved OS with a HR of 0.64 (95% CI, 0.42–0.96). The secondary objective of E+OFS yielded a 7.3% improvement in BCFI over tamoxifen alone. Women under 35 years old seemed to derive the greatest benefit from OFS. The rate of discontinuation at 4 years was 22%. In the OFS group there was an increase in menopausal symptoms, depression, hypertension and osteoporosis.

**TRIAL SUMMARY: Quality of life impact**


This trial is a quality-of-life (QoL) analysis of 1722 premenopausal women with early-stage ER+ breast cancer randomized to adjuvant endocrine therapy with tamoxifen +/- OFS from the SOFT cohort. The analysis was subsequently stratified as well for having received adjuvant chemotherapy prior to endocrine therapy. Parameters such as menopausal symptoms, mood, physical wellbeing, sexual functioning, coping effort and treatment burden were assessed by questionnaire every 6 months up to 24 months, then annually up to 6 years of followup and compared to baseline prior to starting treatment in this intention-to-treat analysis. Short-, intermediate- and long-term side effects were assessed, respectively, at 6, 24 and 60 months postrandomization.

**Results:** Global QoL did not differ after 5 years between the two groups. Patients on T+OFS were significantly more affected by hot flushes at short and intermediate term. The change of hot flushes from baseline improved for T+OFS but not for the T-alone group over the period of 60 months. Patients on T+OFS reported significantly more loss of sexual interest and sleep problems at short term, and more vaginal dryness over the whole treatment period. Patients on T alone reported significantly more vaginal discharge up to 60 months, but only among those patients who did not receive prior chemotherapy. Symptom-specific treatment differences were less pronounced in patients who had received prior chemotherapy. Notably, it seems as though the patients who had received prior chemotherapy had an easier time with coping and lower perceived treatment burden.

**TRIAL SUMMARY: Impact on cognitive function**


Estrogen depletion has long been studied as a factor that can negatively influence cognition. However, the role of ovarian function suppression (OFS) for the treatment of breast cancer in negatively impacting cognition is not well known. This trial enrolled patients from the SOFT trial cohort (3066 premenopausal women with hormone recep-
tor-positive BC randomized to tamoxifen alone vs T+OFS vs E+OFS) to answer this question. Eighty-six of the planned 321 women were recruited to determine whether OFS has an impact on cognition. The study originally intended to look at tamoxifen alone vs T+OFS but, due to poor accrual, the T+OFS and E+OFS groups were pooled. Of the 86 patients, 20 were randomized to T alone, whereas 28 and 26 were randomized to T+OFS and E+OFS, respectively. These patients were asked to complete a brief computerized test battery (CogState) at study entry and 1 year following therapy. The characteristics of the 2 groups were well balanced. The mean age of the participants was 46 years in the T-alone group and 44 years in the OFS group. The majority of patients in both groups had a KPS of 90–100 and most had postsecondary education (over 80% in both groups).

**Results:** There was no significant difference in the change in score from baseline to 1 year between the 2 groups, overall or in each of the 7 cognitive tasks.

**COMMENTARY:** SOFT (Suppression of Ovarian Function Trial) is a randomized trial comparing adjuvant tamoxifen or exemestane plus ovarian suppression versus tamoxifen alone in 3,047 patients in 25 countries. It is the largest randomized trial ever conducted in premenopausal women with hormone receptor-positive breast cancer. Women randomly assigned to ovarian suppression in either arm had the choice of monthly injections of triptorelin (Trelstar), surgical removal of the ovaries, or radiation. These treatments were compared in 2 different groups of women: those who needed chemotherapy (younger age, higher-risk tumours, larger tumours, more likely to be node-positive) and those who did not. Women who had chemotherapy entered the trial 8 months postchemotherapy, while those who did not entered the trial soon after surgery.

Francis et al’s analysis of SOFT data seems to show a benefit from adding OFS to adjuvant therapy for premenopausal women who are at high risk for relapse (younger age, positive lymph nodes, having received chemotherapy). The benefit is modest, with a 7.3% increase in BCFI with hormone receptor-positive breast cancer. Women randomized to ovarian suppression in the adjuvant therapy alone (ZIPP trial and E-3193 trial). In their analysis of data from the SOFT cohort, Ribi et al find that patients who received chemotherapy are the ones who need OFS the most and suffer the least from it, and conclude that in this group the benefits outweigh the toxicity. Nevertheless, the rates of grade 3 or higher toxicity reported in the SOFT trial were greater for the OFS arm at 31.3% vs 23.7% in the T-alone arm, which is not negligible. Patients should be made aware of the potential impact on their quality of life especially in the first 2 years of OFS. It is interesting that the side effects dissipate over the 5 years of treatment. More research would be needed to find out if this is because of physiologic adaptation or because patients have learned to accept this new baseline.

Cognition is thought to be negatively influenced by estrogen depletion. However, Phillips et al, in their sub-analysis of cognitive function in patients enrolled in the SOFT trial, conclude that OFS does not seem to have a profound effect on cognitive status. These results should be interpreted with caution, as the groups studied were small since the study failed to meet its desired accrual. In addition, it is possible that the effects on cognition may be subtle upfront and worsen with time. Given the fact that these patients will need 5 years of therapy, there should be more long-term followup to ascertain whether or not cognition is affected by OFS.

**References**


**Already known:**

- Adding ovarian function suppression (OFS) to hormonotherapy in the adjuvant treatment of breast cancer increases endocrine side effects compared to hormonotherapy alone.

**What these studies showed:**

- There was no significant difference in progression-free survival between tamoxifen (T) alone and T plus OFS.
- Patients who had received prior chemotherapy showed some benefit from the addition of OFS to T.
- OFS increases menopausal symptoms, depression, hypertension and osteoporosis.
- OFS has greatest benefit in women under 35 years old.
- Women who received prior chemotherapy were less bothered by the effects of OFS.
- OFS does not appear to negatively impact cognitive function.

**Next steps:**

- Undertake longer-term followup to assess benefits, quality of life and cognitive function in different subgroups of women who receive OFS along with tamoxifen.