Adding ovarian suppression to tamoxifen for pre-menopausal breast cancer

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SUMMARY

The ASTRAA trial by Kim *et al*. delves into a controversial area in breast oncology—role of ovarian function suppression (OFS) in pre-menopausal women with breast cancer. This question is more relevant in the Indian scenario where the median age of breast cancer is 47 years and a majority of women require chemotherapy as they have locally advanced disease at presentation.[1,2] Even after the publication of the results of three large randomized trials and a meta-analysis,[3–6] the value

of adding OFS to standard therapy is not clear. If we look at the updated results of the SOFT and TEXT trials (reference updated analysis), the benefit of adding ovarian suppression was seen only in patients who required chemotherapy. The other group of patients who were sufficiently low risk not to warrant adjuvant chemotherapy did well irrespective of hormonal therapy regimen. Although distant recurrence-free survival and disease-free survival (DFS) were better with exemestane and OFS compared to OFS and tamoxifen, overall survival showed a reverse trend making interpretation of data difficult. Moreover, toxicity of 5 years of OFS was significant with 30% grade 3–4 toxicity in OFS arms in both SOFT and TEXT trials leading to 25%–30% early discontinuation rates.

In this context, Kim *et al*. tried to answer the question whether benefits of OFS are maintained when duration is reduced to 2 years. They randomized only those patients who received chemotherapy, thus addressing the limitation of SOFT trial in which benefits in overall population might have been underestimated by the good-risk subset of patients not requiring chemotherapy. They also allowed for delayed recovery of ovarian function up to 2 years allowing more patients to be randomized and mimicking the real-world scenario more closely. The trial results showed a 4% DFS benefit in favour of OFS plus tamoxifen over tamoxifen alone. The events were too few to draw any firm conclusions about overall survival.

COMMENT

Although these results indicate that a reduced duration of ovarian suppression may provide the same degree of benefit as extended suppression, a few issues with the trial need to be kept in mind.

First, the authors did not provide any information on the adverse events in both the groups. The major issue with extended ovarian suppression is non-compliance and toxicity, as seen in the SOFT and TEXT trials. The authors reported a 26% discontinuation rate in this trial, which is similar to the SOFT and TEXT trials when OFS was used for 5 years. This rate is higher than expected and difficult to justify in the absence of detailed safety analysis. We have already seen that longer duration of endocrine therapy results in DFS benefit in post-menopausal women.[7] Hence, more data on safety and compliance of reduced duration of OFS are needed before it can be considered standard of care.

Second, the overall DFS in this trial was significantly higher than the matched population of SOFT trial (DFS of 71% and 76% in tamoxifen and tamoxifen+OFS, respectively, in SOFT—almost 15% difference). Since all the patients received chemotherapy in this trial, they were expected to be at a high risk of recurrence and expected DFS was around 70%; this aspect deserved more clarification. A closer look at baseline characteristics suggests that almost 48% of patients had tumours <2 cm and 45% were lymph node-negative; since decision to give chemotherapy varied with institutional practice, it is possible that many low-risk patients got chemotherapy resulting in higher than expected DFS.

Third, the authors used DFS as the primary end-point and overall survival as the secondary end-point, which is acceptable. However, an equally important primary end-point in hormone-positive breast cancer is distant recurrence-free survival as most recurrences are distal (53% in SOFT trial and 70% in this trial). Although an unplanned analysis was done for this end-point and the hazard ratio was significant in favour of OFS plus tamoxifen, we believe it should have been a primary planned analysis.

In the end, we appreciate the work done by Kim *et al*. in this controversial area. Although this trial has some limitations, it is a step in the right direction and longer follow-up might help to clarify the benefit and duration of OFS in women with hormone-positive breast cancer.

Conflicts of interest. None declared

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