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Editorial

New evidence and hope for young patients with breast cancer

In this issue of the *European Journal of Cancer*, another gap in the knowledge base of endocrine and bone-targeted therapy of premenopausal breast cancer patients is closed by the publication of the phase III Hormonal BOne Effects (HOBOE) trial [1]. With more than 1000 patients randomised and more than 5 years of median follow-up, this randomised three-arm trial is an important addition to previous reports on this clinically relevant subject. In summary, it reports a significant disease-free survival (DFS) benefit for the combination of the aromatase inhibitor (AI) letrozole with the bisphosphonate zoledronic acid over tamoxifen (T) (hazard ratio [HR] = 0.52; p = 0.003) in the adjuvant therapy of premenopausal women with hormone receptor–positive breast cancer who are rendered postmenopausal by ovarian function suppression (OFS; using triptorelin in this trial).

HOBOE was started in 2003 with a bone mineral density end-point [2] and amended to an outcome-oriented trial (and confined to premenopausal women) in 2009. The basic structure and statistical planning of the trial were—as in similar contemporary trials in this patient group—relying on more events than those observed. While this is unfortunately limiting the definitiveness of the results of potential pairwise comparisons within this three-arm trial, the magnitude of benefit in the main reported outcome of letrozole plus zoledronic acid over tamoxifen is impressive and, taken together with the SOFT/TEXT [3,4] and ABCSG-12 [5] trial results, confirms the optimal standard of care for these patients.

In addition to the main and protocol-defined results, there are interesting exploratory observations to make from HOBOE. First, while the comparison of Zoledronic Acid plus Letrozole (ZL) vs Letrozol (L) is formally underpowered, the observed HR of 0.7 adds to the body of evidence that 6-monthly zoledronic acid improves outcomes in premenopausal patients with breast cancer on adjuvant OFS. This result is confirming the results of the ABCSG-12 trial [5], and the benefit achieved appears to be larger than the average benefit in the pivotal EBCTCG meta-analysis [6], which did not separately delineate results for premenopausal women on OFS within the 'postmenopausal' group.

In addition, when interpreting the DFS curves of HOBOE with some generosity, one can ascertain the impression that the AI group is clearly better than tamoxifen as long as the drug effect is present, but the L and T curves appear to come together during the 8th year of follow-up. However, the ZL curve remains separated, allowing for a clearly speculative interpretation that the bone effects of the AI vs. tamoxifen may be particularly important for the outcome differences (and only maintained in the bisphosphonate group in which bone turnover is probably reduced permanently [7]).

Adjuvant bisphosphonates are nowadays considered standard therapy for postmenopausal women with hormone receptor–positive breast cancer [8–10], but HOBOE importantly underlines that premenopausal women who are rendered 'postmenopausal' by OFS can benefit from (at least) similar outcome advantages.

While clearly extreme caution has to be used to avoid overinterpreting HOBOE subgroup results (no significant interactions except HER2 status), it is interesting to note that the letrozol + zoledronic acid versus tamoxifen effect appears to be driven by patients who were younger than 40 years, were not overweight and did not receive additional chemotherapy. Particularly, the body mass index observation confirms with previously reported results that the AI may be less effective in overweight premenopausal women even in the presence of OFS [11]; however, this remains controversial.

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In general, HOBOE confirms the excellent long-term outcomes of premenopausal women with luminal breast cancer when treated optimally [12]. With an estimated 10-year overall survival of more than 90 percent (despite approximately half of the trial patients being node positive), the myth of general 'high risk' just because of young age can finally be put to a definitive rest, which is certainly reassuring both for patients and caregivers.

What are the implications of the HOBOE results for daily clinical practice? While SOFT and TEXT have defined that premenopausal patients with low-risk luminal breast cancer are adequately treated with adjuvant tamoxifen, HOBOE confirms that the combination of OFS with an AI plus a bone-modifying agent should be used for patients with any sign of increased risk for relapse. The main side-effect of effective oestrogen deprivation by OFS and aromatase inhibition particularly in premenopausal women is bone loss [13], which can be effectively prevented by the addition of antiresorptive treatment that in addition improves DFS.

While HOBOE is not reporting any fractures (which could indicate some underreporting; however, fractures are fortunately not frequent in this age group), the ongoing follow-up of the trial will provide the opportunity to study the long-term effects of severe oestrogen deprivation with and without bone-targeted therapy in this young patient group. In postmenopausal patients, adjuvant treatment with the anti−RANK-Ligand antibody denosumab dramatically reduces fractures [14] and is generally believed to be more effective than bisphosphonates with respect to that end-point [15]. In addition, it was recently demonstrated that adjuvant denosumab also improves DFS in a similar manner as bisphosphonates [16]. There are, however, no adjuvant denosumab data available specifically for premenopausal patients.

In summary, HOBOE confirms both the adjuvant use of an AI and a bisphosphonate in addition to OFS for premenopausal patients with hormone receptor−-positive HER2-negative breast cancer, which has also been defined as a standard of care by the most recent St. Gallen/Vienna Consensus Conference [9]. As always, the potential benefits and burden of adjuvant therapies for individual patients have to be weighed carefully based on individual risk and tolerability assessments.

Conflict of interest statement

Professor Gnant has received institutional research support from AstraZeneca, Roche, Novartis and Pfizer and has received lecture fees, honoraria for participation on advisory boards and travel support from Amgen, AstraZeneca, Celgene, Eli Lilly, Invectys, Pfizer, NanoString, Novartis, Roche and Medison. He has served as a consultant for AstraZeneca and Eli Lilly, and an immediate family member is employed by Sandoz.

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