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E28. Breast tolerance, tibolone compared with other hormonal treatments

Hakan L. Olsson *

Department of Oncology, University Hospital, Lund S-221 85, Sweden

A number of recent studies have found that the risk of breast cancer is augmented by the use of hormonal treatment (HT), as a combined therapy with oestrogen and progestins (EPT). Nevertheless, the amplitude of the risk and the mortality risk remain a matter of debate.

Worldwide, an increase in peri- and post-menopausal breast cancer incidence has been noted when compared with the incidence noted 50 years ago. This increase can be due to the changes in parity and to the age at first pregnancy, to the increase in mammographic screening, to the use of hormonal contraception with high dosages, and due to the use of HT after the menopause.

The risk, attributed to EPT, has been associated with current use and neither the dose, type of administration, type of progestin or therapy schedule (continuous combined or continuous sequential) have modified these findings. This risk seems to be independent of other risk factors of breast cancer (such as parity, age at menarche, age at first full-term pregnancy and family history of breast cancer), except for weight. Lean women show a higher risk than other women [1,2].

However,the overall cancer incidence after HT use is not increased due to the fact that HT reduces the risk of colon cancer and, possibly, smoking-related cancers [3,4]. Looking at women using EPT, the strong effect on breast cancer may lead to a slight increase in the total cancer incidence, although risk reductions can be seen for some tumour sites.

Studies suggested that the breast cancer that develops in association with HT is of a low malignant grade. These tumours have a better prognosis and this implies that the development of each tumour may follow, at least partly, a distinct pathway of evolution, according to the parent's age, tumour proliferation rate and cell biology at the moment of initiation [5].

However, in the most recent study, the Women's Health Initiative (WHI) randomised trial, the breast cancer type associated with EPT use was less favourable (tumours were larger and at a more advanced stage) than in the control group not using HT; oestrogen plus progestin may stimulate breast cancer growth and the higher breast density can hamper breast cancer diagnosis [6,7]. In some studies, it is suggested that the histological breast cancer type, lobular carcinoma, has a stronger risk relationship with hormone replacement therapy (HRT) use than ductal carcinoma.

If we consider mortality, there was no difference in the WHI study between the treatment and placebo groups, while in some observational studies, the survival rate was better in female users of HT, independent of mammographic screening. These studies may have inherent biases that affect their interpretation, so there is a need for more good prospective survival data.

Whether there is a risk of breast cancer after use of oestrogen only (ET) or use of tibolone is less clear.

The large Million Women Study in the United Kingdom (UK) [8] suggests that there is a slight increase in risk after the use of oestrogens or tibolone, while previous studies have not clearly shown that. The small number of tibolone users so far included in cohort studies may inherently carry high-risk factors for breast cancer, such as a family history of the disease. Assuming that a third of women using tibolone have a family history compatible with breast cancer, the Relative Risk (RR) for the whole group should be 1.33. However, results regarding tibolone, in particular, are as yet, difficult, to interpret.

For all HRTs, as well as for tibolone, results can be influenced by some biases (information, surveillance, recall); the use of mammographic screening and the type of instrument used to collect exposure information may impact upon the magnitude of these biases.

* Tel.: +46 46 177554; Fax: +46 46 147327.
E-mail address: hakan.olsson@onk.lu.se.

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In summary, the use of progestin-containing HTs is associated with quite a high risk of breast cancer and the risk increases with a longer duration of use. There is little evidence as yet to suggest that there is a large difference in breast cancer risk between combined continuous and combined sequential therapy. The risk association disappears after 5 years of non-use.

Oestrogen use only or treatment with tibolone is associated with a much lower risk, if any.

In the future, further results of randomised controlled trials (RCTs) are needed but, meanwhile, it may be possible to assess breast cancer risk in association with HT by use of surrogate markers of breast cancer, such as breast density or breast epithelial proliferation. Early data from such studies suggest that increased breast density as a marker of increased risk is seen in women using combined oestrogen and progestin therapy. An adverse event from use of combined HT is that an increased mammographic density, which is seen in many women, also reduces the sensitivity of tumour detection by mammography.

Tibolone or oestrogen only therapy do not seem to substantially increase breast density.

Epithelial proliferation in the breast can also be considered as an unwanted effect of hormonal treatment and, possibly, a marker of the breast cancer risk. A continuous combined EPT significantly increases the proliferation of mammary epithelial cells in postmenopausal woman [9,10]. With tibolone, there is no increase of proliferation in the mammary gland of primates [11]. We are awaiting data in women.

Other markers of breast tolerance to hormone medications, such as breast pain or changes in breast volume, need to be assessed further in relation to risk.

The surrogate measures, such as mammographic breast density and breast epithelial proliferation (and breast pain), may predict which agents are associated with a high breast cancer risk; new agents introduced to the market should document such effects before approval by governmental agencies. Similarly, studies should be done assessing whether the risk associated with progestin-containing HTs is concentrated in women showing increased mammographic breast densities, epithelial proliferation in the breast or tenderness in the breast during therapy.

Our present knowledge on the adverse health events, especially those associated with EPT use, enable suggestions to be made on how to avoid the breast cancer risk by using oestrogen therapy only in hysterectomised women and in women with an intact uterus either using tibolone or a low-dose progestin intrauterine device (IUD) with oestrogen given orally or as a patch, but such association also needs to be investigated further for its safety profile.

Therapy in women should be individualised and prescribed at and for an optimal time. Such therapies given for less than four years have been associated with negligible increases in breast cancer risk. Preferably, the patient on such therapy should also be monitored by mammography to detect signs of increased density.

It is unclear how these data transfer to women who have already had breast cancer and need HRT. In the HABITS study (stopped) [12], early data suggest that progestin-containing therapy is harmful, but this differs to data reported in the Stockholm study (RR=0.82, 95% Confidence Interval (CI) 0.35–1.89). This study has also been stopped due to anticipated difficulties in recruitment and compliance. For use of oestrogen only or tibolone definitive answers are still needed.

Research into safe and effective therapies to relieve menopausal complaints among women with a personal history of breast cancer, such as those in LIBERATE study, has to be continued and supported by physicians for recruitment.

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