Breast Cancer Chemoprevention – not yet There

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In principle, disease prevention using pharmacological intervention would be a highly attractive concept in a malignant disease as common as breast cancer: Despite recent advances in early detection and treatment and even a recently observed decline in mortality rates in several countries, breast cancer remains one of the main causes of death in women. Thus, preventing the potentially deadly disease could prove more effective than treating it, saving affected patients the threat for their lives and the deterioration of their quality of life both by the disease itself and by the necessary treatment as well as avoiding the cost of treatment for society.

However, chemoprevention of breast cancer comprises interventions that need several characteristics to be successful: The clear-cut identification of a subgroup of healthy women who are at particular risk, established evidence for superior efficacy of the intervention as compared to its side effects, and a favorable toxicity and tolerability profile of the drugs used in order to reach acceptance by women. Unfortunately, none of these aims have so far been reached convincingly, making breast cancer chemoprevention an example of a scientifically level-one proven intervention that has in general not been accepted in clinical practice.

The failure of drugs that have been tested for breast cancer prevention has different reasons: Retinoids have been assessed as preventive agents for several tumor entities including breast cancer. In particular, fenretinide was evaluated because of its potential impact on the development on contralateral breast cancer in the adjuvant setting with no overall effect [1]. In any case, because of the side effect profile of these substances, their general use cannot be recommended [2].

Because of the proven activity of selective estrogen receptor modulators (SERMs) in invasive breast cancer and ductal carcinoma in situ (DCIS), the use of SERMs for chemoprevention appears to be logical. Tamoxifen is probably the best-evaluated anti-cancer agent with many millions of treatment

years on record. In preclinical studies, tamoxifen was also very potent in preventing both development and growth of breast cancer cells [3]. To date, 4 large clinical prevention trials have been reported assessing the chemopreventive potential of tamoxifen: the Italian trial [4] randomized 5,408 women to tamoxifen versus placebo, not requiring increased breast cancer risk for inclusion in the trial but confining accrual to hysterectomized women and thus avoiding one of the major side effects of tamoxifen. There was no difference in the overall incidence of breast cancer compared with the placebo group after a median follow-up of 81.2 months [5]. A British Trial at the Royal Marsden Hospital [6] randomized 2,494 women at increased risk (determined mainly by family history of breast cancer) without significant benefit. The largest trial was reported by the National Surgical Adjuvant Breast and Bowel Project [7] which randomized a total of 13,388 women with increased risk according to the Gail model. In this trial, the treatment with tamoxifen resulted in a significantly lower risk of invasive carcinoma by 49% and a significantly lower risk for non-invasive cancer by 50% after a follow-up of 4.5 years. Recently, the results of the International Breast Cancer Intervention Study were published [8], reporting on 7,152 women randomized to preventive tamoxifen versus placebo. While a meta-analysis of the tamoxifen studies identified an overall risk reduction of 38% for preventive tamoxifen administration [9], this benefit was outweighed in by an excess in morbidity and mortality, particularly pulmonary embolism.

In general, the greatest benefit of tamoxifen prevention appears to exist in younger women, hysterectomized women, and women at higher risk. The American Society of Clinical Oncology has concluded on a consensus panel that tamoxifen 20 mg/d for 5 years ‘may be offered to women with a defined 5-year projected breast cancer risk of 1.66%’ – whatever that may mean to women in daily practice [10]. It was also stated

that there is no simple scale to weigh the disparate clinical outcomes reported, making this conclusion unsuitable for defining a clinically useful state-of-the-art guideline. In order to be useful for the majority of women, the mathematical risk reduction of preventive tamoxifen needs to be translated into absolute figures for individual women, an exercise that still could not be mastered successfully.

Also for another SERM, raloxifene, the general conclusion based on currently available evidence is that to date there is no general recommendation for its use for breast cancer chemoprevention, although raloxifene led to a significant reduction in risk of invasive breast cancer in the multiple outcomes of raloxifene evaluation (MORE) trial, an osteoporosis treatment study conducted in postmenopausal women assumed to have a normal to low-risk of developing breast cancer [11]. In contrast to tamoxifen, the risk for endometrial cancer or vaginal bleeding was not elevated in raloxifene-treated patients [12]. The national surgical breast and bowel project (NSABP) performed the study of tamoxifen and raloxifene (STAR) trial in order to assess the preventive use of raloxifene compared to tamoxifen for reduction of incidence of invasive breast cancer in postmenopausal women at high risk for the disease [14]. A total of 19,747 patients were enrolled, and raloxifene displayed the ability to reduce the risk of invasive breast cancer similar to tamoxifen, but with lower risk of thromboembolic events and fewer hysterectomies and cataracts, however, the drug failed because of an observed in-

creased risk of non-invasive breast cancer [15]. The risk for stroke, ischemic heart disease and fractures was similar for both drugs [16].

For the palliative and adjuvant treatment of breast cancer, third generation aromatase inhibitors have been established as the new standard of care. Based on their improved efficacy and better tolerability they are currently also investigated for chemoprevention. Since early clinical results from the huge arimidex, tamoxifen, alone or in combination (ATAC) trial demonstrate a beneficial effect of aromatase inhibition on the (secondary) prevention of contralateral cancers [17], their potential for chemoprevention is promising. The ongoing global international breast cancer intervention study (IBIS) II trial will prospectively evaluate the risks and benefits of anastrozole in a preventive approach.

In summary, chemoprevention of breast cancer is still a research field with many open questions. Despite several large and expensive clinical prevention trials, the overall results have been discussed controversially indicating that the cost benefit ratio of the intervention is not convincing. Also, we still lack the ability to reliably define who is at increased risk and may benefit most from chemoprevention. Advances in molecular diagnosis and methodology may change this in the future. Until we will be able to accurately predict individual risk, at least to some extent, and intervene with acceptable toxicity, breast cancer chemoprevention remains a dream that does not touch ground in everyday clinical practice.

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