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Chemoprevention of breast cancer: The European and Australian IBIS and other trial experience with aromatase inhibitors

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Chemoprevention of breast cancer: The Italian experience with retinoids and low-dose tamoxifen

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Tamoxifen, a selective estrogen receptor modulator, is FDA approved for breast cancer risk reduction in women at high risk according to the Gail model and in women with previous LCIS or DCIS (LIN1–3 and DIN 1c, 2, 3). However, use of tamoxifen in the clinics is hampered by serious adverse events attributable to the partial estrogenic activity of the drug, such as increased risk of endometrial cancer and of venous thromboembolism. These adverse events have significantly limited the broad use of tamoxifen in chemoprevention.

To improve the risk-benefit ratio, the use of lower doses of the drug has been proposed. Recent trials from our groups (Decensi et al. 2003, 2007; Guerrieri-Gonzaga et al. 2006) have shown that the standard dose of 20 mg/day can be reduced without loss of activity. Specifically, a dose reduction up to 1 mg/day retained tamoxifen antiproliferative activity on breast cancer cells in women treated for 4 weeks before surgery (Decensi et al. 2003). By contrast, treatment with tamoxifen for 1 year the range of 1–5 mg did not increase endometrial proliferation assessed by Ki-67 compared with placebo in HRT users. Interestingly, Ki-67 (Decensi et al. 2007) is a marker of endometrial cancer risk, and the risk endometrial cancer under tamoxifen is dose dependent. Importantly, low doses of tamoxifen are associated with a decrease of its estrogenic activity on a variety of biomarkers of estrogenicity, including IGF-I, SHBG and antithrombin-III, with a potential decrease of venous thrombotic events. The use of HRT in women aged 60 years or younger has recently been found to be beneficial in the WHI, with a significant decrese in cardiovascular mortality. We are currently conducting a phase III trial of tamoxifen 5 mg day in women on HRT (HOT study) to assess the efficacy of this combined approach in recent postmenopausl women to retain benefits while reducing the risks of either agent.

The rationale for a dose reduction is further supported by the recent results of a randomized double-blind 2×2 trial of low-dose tamoxifen and fenretinide (Guerrieri-Gonzaga et al. 2006) for breast cancer prevention of high risk premenopausal women, where tamoxifen 5 mg/day and fenretinide given alone show promising activity in premenopausal breast cancer prevention, although their combination may be adverse (Decensi et al. 2009). Importantly, tamoxifen lowers IGF-I more profoundly in women with prior IEN than in unaffected women selected by the Gail model and decreases mammographic density like the standard dose, whereas fenretinide has antiestrogenic effects at uterine level. Circulating IGF-I is a risk biomarker for breast cancer. Tamoxifen also exhibits a high tissue distribution, and it has been shown that the dose of 5 mg/day attains, at the breast tissue level, a concentration 10 times higher than that needed to inhibit cell growth in vitro. The results of fenretinide at 20 years continue to show a benefit in terms of reduction of contralateral and ipsilateral breast cancer occurrence in premenopausal women. A trend to a lower risk of ovarian cancer was observed during the 5 year intervention period. A phase III trial in BRCA carriers will start shortly.

The optimal duration of tamoxifen treatment is also unclear. The recent results of the IBIS trial however show that the effect of tamoxifen is durable after 5 years from treatment completion, thus suggesting the attainment of a true preventive effect, not simply a regression of subclinical disease. This provides the background for a shorter treatment, to minimize toxicity, possibly followed by cyclical, intermittent courses. A phase III trial of low dose tamoxifen in women with prior DIN or LIN has been launched by our group.

Reference(s)

Decensi A, Robertson C, Viale G, Pigatto F, Johansson H, Kisanga ER, Veronesi P, Torrisi R, Cazzaniga M, Mora S, Sandri MT, Pelosi G, Luini A, Goldhirsch A, Lien EA, Veronesi U (2003) A randomized trial of low-dose tamoxifen on breast cancer proliferation and blood estrogenic biomarkers. *J Natl Cancer Inst* 95: 779–90.

Decensi A, Gandini S, Serrano D, Cazzaniga M, Pizzamiglio M, Maffini F, Pelosi G, Daldoss C, Omodei U, Johansson H, Macis D, Lazzeroni M, Penotti M, Sironi L, Moroni S, Bianco V, Rondanina G, Gjerde J, Guerrieri-Gonzaga A, Bonanni B (2007) Randomized dose-ranging trial of tamoxifen at low doses in hormone replacement therapy users. *J Clin Oncol*; 25: 4201–09.

Decensi A, Robertson C, Guerrieri-Gonzaga A, Serrano D, Cazzaniga M, Gulisano M, Johansson H, Cassano E, Moroni S, Pelosi G, Johnson K, Bonanni B (2009) *J Clin Oncol* 27: 3739–56.

Guerrieri-Gonzaga A, Robertson C, Bonanni B, Serrano D, Cazzaniga M, Mora S, Gulisano M, Johansson H, Formelli F, Intra M, Latronico A, Franchi D, Pelosi G, Johnson K, Decensi A (2006) Preliminary results on safety and activity of a randomized, double-blind, 2×2 trial of low-dose tamoxifen and fenretinide for breast cancer prevention in premenopausal women. *J Clin Oncol* 24: 129–35.

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Chemoprevention of hormone receptor-negative breast cancer: new approaches needed

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Results from clinical trials have demonstrated that is possible to prevent estrogen-responsive breast cancers by targeting the estrogen receptor with selective estrogen receptor modulators (SERMs, such as tamoxifen, raloxifene, or lasofoxifene), or with aromatase inhibitors (anastrozole, letrozole, or examestane). Results from breast cancer treatment trials suggest that aromatase inhibitors may be even more effective at preventing breast cancer than are SERMs. However, while SERMs and aromatase inhibitors do prevent the development of many ER-positive breast cancers, these drugs do not prevent ER-negative breast cancer. These results show that new approaches are needed for the prevention of this aggressive form of breast cancer. Our laboratory and clinical efforts have been focused on identifying critical molecular pathways in breast cells that can be targeted for the prevention of ER-negative breast cancer. Our preclinical studies have demonstrated that nuclear receptors such as RXR receptors and vitamin D receptors are critical for the growth ER-negative breast cells and for the transformation of these cells into ER-negative cancers. Other studies show that growth factor pathways (including those stimulated by EGFR, Her2, or IGFR overexpression or activation) are activated in many ER-negative breast cancers, and that these pathways can be targeted for the prevention of ER-negative breast cancer in mice. Clinical studies have also shown that PARP inhibitors are effective for the treatment of breast cancers