S16. Is Low-Dose Tamoxifen a Reasonable Alternative?

Andrea Decensi

European Institute of Oncology, Milan, and E.O. Ospedali Galliera, Genoa, Italy

Tamoxifen, a selective estrogen receptor (ER) modulator, lowers mortality in patients with ER positive breast cancer and breast cancer incidence in healthy women at increased risk. However its partial estrogenic activity is an important limiting factor which has been associated with drug resistance in advanced disease and with a detrimental trend after treatment for a period longer than 5 years in the adjuvant setting. Although the agonistic activity of tamoxifen reduces osteoporotic bone fracture, a higher risk of endometrial tumors, including rare cases of uterine sarcomas, and venous thromboembolic events is consistently observed across studies. Several factors influence the complex antagonist/agonist effects of tamoxifen in humans, including differences in target tissue ER co-regulator recruitment, endocrine milieu, dose, and duration of exposure. For instance, no significant excess of endometrial cancer and venous thromboembolic events is observed in premenopausal women or women on hormone replacement therapy. Furthermore, there is evidence that the endometrial cancer risk is time- and dose-dependent. While tamoxifen is the prototype of a designer drug which acts through binding to a specific molecular target, the ER, following saturation kinetics, its early clinical development has been characterized by the search of the maximum tolerated dose rather than the optimal biological dose. However, efficacy was similar between 20 mg/day and higher doses in lowering recurrence and mortality for breast cancer, and results from animal studies have suggested that a further dose reduction up to 1 mg equivalent human dose could in fact retain a complete inhibitory activity on mammary tumor formation.

In a recent trial, we assessed the antiproliferative activity of 5 mg/day and 1 mg/day of tamoxifen in comparison with the conventional dose of 20 mg/day in a pre-operative setting, using change in breast cancer tissue expression of the proliferation antigen Ki-67 as a surrogate endpoint of anti-tumor effect, inasmuch as pre-operative studies have demonstrated that the reduction of Ki-67 expression predicts the clinical response to hormonal agents in breast cancer. In addition, we measured an array of circulating biomarkers associated with risk for different diseases, including insulin-like growth factor-I (IGF-I) and sex-hormone binding globulin (SHBG) for pre- and postmenopausal breast cancer; cholesterol, triglycerides, fibrinogen and C-reactive protein for coronary heart disease; fibrinogen and antithrombin-III for venous thromboembolic events; and peptide bound collagen type-I cross-linked C-telopeptide (C-telopeptide) for bone osteoporotic fractures. These circulating biomarkers, of which IGF-I was the primary measure, are modulated by tamoxifen mainly as a result of its estrogenic activity on different target systems and therefore are suitable endpoints to assess dose-response relationships.

We randomly assigned 120 women with estrogen receptor (ER) positive breast cancer to either 1, 5 or 20 mg/day of tamoxifen for four weeks prior to surgery. All women received 20 mg on day-1. Drug concentrations were measured in serum and cancer tissue. There were two non-randomized control groups: 34 women with ER-negative biopsy were recruited concurrently, while 29 women with ER-positive tumors who would have been eligible were recruited after randomization completion. Proliferation in the re-excision specimen was reduced in all three tamoxifen groups, but there was no difference in the magnitude of reduction among groups (p=0.81). Relative to baseline, median percent Ki-67 changes were: 1 mg, -14.0% (95% confidence interval [CI], -38.8% to 0%); 5 mg, -11.7% (95% CI, -32.0% to 8.5%); 20 mg, -15.6% (95% CI, -44.5% to 14.1%). The non-randomized control groups demonstrated an increase in proliferation. Relative to baseline, Ki-67 increased by 18.6% (95% CI, -3.3% to 33.0%) in ER-positive controls and by 12.7% (95% CI, 0% to 19.6%) in ER-negative controls. Tissue drug concentrations at the lowest dose tested were within the inhibitory concentration range for MCF-7 cells. A dose-response relationship was noted for several serum biomarkers, including reduction in IGF-I, an increase in SHBG, a decrease in LDL-cholesterol, C-reactive protein, fibrinogen and antithrombin-III.

We conclude that doses of 1-5 mg/day of tamoxifen are comparable to standard 20 mg on cancer proliferation. Tamoxifen at low doses may improve its therapeutic index and should be assessed further.