S16. HRT Opposed by Tamoxifen (HOT Study): Rationale and Design

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While life expectancy has grown by approximately 30 years in the last century in western countries, the age at menopause has increased by 2-3 years only. Thus, women are exposed to postmenopausal symptoms and disorders for a considerable period of their lifetime, and the management of these frequent disorders is an important public health issue. Since women taking HRT represent a self-selected cohort at higher risk for breast cancer, ethical issues concerning the risk of an excessive medical intervention by the use of chemopreventive agents are less relevant in this population.

A number of different observations indicate that the combination of HRT and a selective estrogen receptor modulator (SERM) such as tamoxifen may retain the benefits while reducing the risks of either agent. Prolonged use of HRT increases the risk of developing breast cancer, mostly estrogen receptor positive, particularly with the combination of estrogens and progestins. The increased risk has been associated with an increased expression of estrogen receptors in the healthy breast tissue, thus leading to an enhanced sensitivity to the estrogen signal. Moreover, reproductive factors such as early menarche and delayed pregnancy are also associated with a higher risk of estrogen receptor (ER) positive breast cancer. Thus, the addition of a SERM may reduce the hormone growth promoting effect on the breast gland. A *post hoc* analysis after 7 years of follow-up of the Italian study of tamoxifen in hysterectomized women shows a 60% lower risk of breast cancer in the tamoxifen arm in the subset of 1580 women who ever used HRT (mainly transdermal unopposed ERT) before and/or during the trial.

Recent studies suggest that the standard dose of tamoxifen may be reduced to one quarter without significant loss of its beneficial biological effects. Since the endometrial effect of tamoxifen is dependent on treatment duration, cumulative dose and, possibly, daily dose, a dose reduction could substantially reduce the risk of endometrial cancer while retaining its preventive efficacy.

On the other hand, the addition of HRT containing progestins could also minimize the risk of endometrial cancer associated with tamoxifen. Moreover, estrogen should reduce the incidence of vasomotor and urogenital symptoms, which are a major reason for tamoxifen withdrawal in the prevention studies. Notably, in the NSABP prevention trial, women aged 50 or younger demonstrated no significantly increased incidence of severe adverse events, including endometrial cancer and venous thromboembolic events. One possible explanation for the lack of severe toxicity in premenopausal women is the concomitant presence of adequate circulating estrogen levels which prevent tamoxifen from acting as an estrogen agonist on these target tissues. In this regard, our current data from the tamoxifen trial show no evidence of an additive effect of tamoxifen and ERT on the risk of venous thromboembolic events.

Our results strongly suggest that tamoxifen significantly reduces the risk of breast cancer in ERT users. A new phase III trial has therefore been implemented: the HOT (Hormone replacement therapy Opposed by low dose Tamoxifen) Study where a total of 8500 women on HRT will be randomized to either placebo or tamoxifen 5 mg/day for 5 years.