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Tamoxifen versus toremifene in the adjuvant treatment of breast cancer

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1. Introduction

Toremifene, developed in the 1980s, is a triphenylethylene drug which binds to the Oestrogen Receptors (ERs). It may exert oestrogenic or anti-oestrogenic effects or both depending on the dose and duration of treatment, the target organ chosen, or the endpoint used [1]. Toremifene has been found to have comparable anticancer efficacy to that of tamoxifen in metastatic breast cancer, and it has, in general, a similar side-effect profile [2].

2. Study design

The Finnish Breast Cancer Group initiated in 1992 a randomised, prospective trial where these two anti-oestrogens were compared as adjuvant treatment for postmenopausal women with axillary node-positive breast cancer. In this multicentre trial, toremifene given at the dose of 40 mg/day was compared with tamoxifen used at the standard dose of 20 mg/day for 3 years. A total of 1480 patients (toremifene, $n=751$; tamoxifen, $n=729$) were accrued to the trial from 1992 to 1999. The scheduled safety and early efficacy data were analysed when the last randomised patient was followed-up for at least 1 year. The mean follow-up time was 4.4 years (2:2–9.2 yrs).

3. Results

The two groups were well balanced with respect to patient or disease characteristics. The breast cancer recurrence rate was 22.2% ($n=160$) in the toremifene arm and 24.2% ($n=171$) in the tamoxifen group ($P=0.42$). When only patients with ER-positive cancer were analysed ($n=1153$), the risk of breast cancer recurrence did not differ between the two arms, the Hazard Ratio among the toremifene-treated women was 0.96 (90% Confidence Interval (CI) 0.89–1.09, $P=0.51$). The mean time to recurrence and overall survival rates were also similar in both groups.

The subjective side-effect profiles were similar in both treatment groups. The most common treatment-related adverse effect was sweating, which was recorded at least once during the follow-up in 53.8% of the toremifene-treated women and in 51.1% of the tamoxifen-treated patients ($P=0.42$). Sweating and hot flashes were most commonly observed during the first 6 months of therapy. A significant difference between the drugs was the presence of a higher incidence of leucorrhea in patients treated with toremifene (42.0% versus 35.5%, $P=0.05$). The frequency of weight gain of more than 5% of the pretreatment body weight was similar in both groups (5.0% versus 4.4%). Such weight gain increased with continued treatment, but in both arms the body weight returned to the entry level within the first 6 months following the 3-year treatment period.

The incidence of thromboembolic events was slightly higher in the tamoxifen group than in the toremifene group, but the difference was not significant (5.9% versus 3.5%, respectively, $P=0.11$). Bone fractures were recorded more commonly in the toremifene group (2.8%) than in the tamoxifen (1.1%) group ($P=0.09$). The incidence of second cancers did not differ significantly between the study arms.

The present data, based on a median follow-up time of 4.4 years and 1480 postmenopausal women, suggest that the efficacy of adjuvant toremifene 40 mg/day is not inferior to that of 20 mg/day of tamoxifen in preventing breast cancer recurrence [3].

Tamoxifen and toremifene have the dual anti-oestrogenic and oestrogenic actions. The main effect on breast tissue is anti-oestrogenic, whereas many of the other effects, such as those on the uterus, lipid metabolism, vasculature, blood haemostasis, and bone resorption are considered to be oestrogenic-agonistic. Some preclinical data suggest that toremifene may have a lower oestro-

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genic-to-antiestrogenic ratio than tamoxifen, which might explain some of the differences between these agents in the present trial. The optimal dose of toremifene in the adjuvant setting is not known. In one study in metastatic breast cancer patients, oral daily toremifene doses of 20, 40 and 60 mg were compared for efficacy, but no difference between the 40 and 60 mg doses was found with respect to the cancer response rates [4]. In the present study, we used 3-year adjuvant treatment, which was common practice in Finland when the trial was started. An overview has found 5 years of adjuvant tamoxifen therapy to be superior to 2 years or less [5], but more data may be needed to confirm the superiority of 5 years of tamoxifen or toremifenne over 3-year therapy.

4. Conclusions

The side-effect profile of toremifene resembles that of tamoxifen, and the anticancer efficacy of toremifene appears to be no less than that of tamoxifen in the adjuvant treatment of postmenopausal, node-positive breast cancer. It is possible that toremifene has less oestrogenic effects than tamoxifen, which might explain the trends observed in the frequency of thromboembolic events and bone fractures.

References

1. Kangas L, Kallio S, Blanco G. A new triphenylethylene compound, FC-1157a:II. Antitumour effects. *Cancer Chemother Pharmacol* 1986, **17**, 109–114.
2. Homesley HD, Shemano I, Gams R, *et al*. Antiestrogenic potency of toremifene and tamoxifen in postmenopausal woman. *Am J Clin Oncol* 1993, **16**, 117–122.
3. Holli K, Valavaara R, Blanco G. Safety and efficacy results of a randomized trial comparing adjuvant toremifene and tamoxifen in postmenopausal patients with node-positive breast cancer. *J Clin Oncol* 2000, **18**, 3487–3494.
4. Ellmen J, Werner D, Hakulinen P, *et al*. Dose-dependent hormonal effects of toremifene in postmenopausal breast cancer patients. *Cancer Chemother Pharmacol* 1998, **45**, 402–408.
5. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: An overview of the randomized trials. *Lancet* 2000, **351**, 1451–1467.