Toremifene and tamoxifen are equally effective for early-stage breast cancer: first results of International Breast Cancer Study Group Trials 12-93 and 14-93

International Breast Cancer Study Group\(^1\)*†

\(^1\)See Appendix for the names and affiliations of the participants and authors of the International Breast Cancer Study Group Trials 12-93 and 14-93

Background: Toremifene is a chlorinated derivative of tamoxifen, developed to improve its risk–benefit profile. The International Breast Cancer Study Group (IBCSG) conducted two complementary randomized trials for peri- and postmenopausal patients with node-positive breast cancer to compare toremifene versus tamoxifen as the endocrine agent and simultaneously investigate a chemotherapy-oriented question. This is the first report of the endocrine comparison after a median follow-up of 5.5 years.

Patients and methods: 1035 patients were available for analysis: 75% had estrogen receptor (ER)-positive primary tumors, the median number of involved axillary lymph nodes was three and 81% received prior adjuvant chemotherapy.

Results: Toremifene and tamoxifen yielded similar disease-free (DFS) and overall survival (OS): 5-year DFS rates of 72% and 69%, respectively [risk ratio (RR) = 0.95; 95% confidence interval (CI) = 0.76–1.18]; 5-year OS rates of 85% and 81%, respectively (RR = 1.03; 95% CI = 0.78–1.36). Similar outcomes were observed in the ER-positive cohort. Toxicities were similar in the two treatment groups with very few women (<1%) experiencing severe thromboembolic or cerebrovascular complications. Quality of life results were also similar. Nine patients developed early stage endometrial cancer (toremifene, six; tamoxifen, three).

Conclusions: Toremifene is a valid and safe alternative to tamoxifen in postmenopausal women with endocrine-responsive breast cancer.

Key words: adjuvant therapy, early-stage breast cancer, tamoxifen, toremifene

Introduction

Several studies have reported the value of adjuvant chemo-endocrine treatment in the management of postmenopausal patients with node-positive early breast cancer [1–7]. Endocrine responsiveness is currently recognized as the most useful prognostic and predictive tool to design tailored treatment options in different patient subpopulations [8]. Tamoxifen is still the antiestrogen of choice [9], but several endocrine options are under investigation and will become available in the near future [10, 11]. Concern about the side-effects of tamoxifen, in particular thromboembolic events, endometrial cancers and ocular toxicity, has led to the development of several analogs including toremifene, a chlorinated derivative with similar site-specific activity. In preclinical studies it has been shown to have equivalent estrogen receptor (ER) binding and anti-tumor efficacy [12, 13], with less estrogenic activity and DNA adduct formation in the endometrium [14–18]. Tamoxifen and toremifene induce similar estrogenic effects on the endometrium in postmenopausal women [19, 20], but conclusive data on the uterine carcinogenic effect of toremifene are not yet available due to the limited number of long-term users in prospective clinical trials [21]. No excess risk of endometrial cancer has been reported in the marketed use of toremifene so far [22, 23]. In contrast to tamoxifen [24], and despite its pharmacological similarity and the high dose administered in some trials, toremifene has not been associated with severe ocular toxicity [25].

Both tamoxifen and toremifene reduce serum total cholesterol and low density lipoprotein (LDL) levels. In contrast to tamoxifen, toremifene may increase serum high-density lipoprotein but not triglyceride levels, a finding that could translate into a better anti-atherogenic effect [26–28]. The impact of these changes on coronary artery disease risk is...