



Do we need another selective estrogen receptor modulator for the adjuvant treatment of breast cancer?

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In this issue of *Current Oncology*, Qin and colleagues¹ from the Sun Yat-sen University Cancer Centre in Guangzhou, China, report their experience using toremifene as adjuvant treatment for 396 premenopausal women with early endocrine-responsive breast cancer at a mean follow-up of 6.9 years. The reported outcomes for disease-free and overall survival are similar to those of the 1451 patients who received tamoxifen.

Why should we take note? After all, tamoxifen is the selective estrogen receptor modulator (SERM) of choice in Canada, a practice supported by robust data. The latest meta-analysis of more than 10,000 women of all ages with early breast cancer who participated in randomized controlled trials of 5 years of adjuvant tamoxifen compared with placebo confirms a reduction of breast cancer recurrence rates by half and of breast cancer-specific mortality by one third at 5 years' follow-up². The meta-analysis also demonstrates a strong effect for the 2614 women younger than 45 at study entry: relative risk reductions of 42% for breast cancer recurrence and 25% for breast cancer mortality. Furthermore, a beneficial effect of tamoxifen persists at 10 and 15 years.

Toremifene, a nonsteroidal triphenylethylene SERM differs from tamoxifen by the addition of a single chlorine side chain. A recent Cochrane review³ endorsed toremifene as an alternative to tamoxifen in the first-line treatment of endocrine-responsive advanced breast cancer in postmenopausal women. Marketed under the brand name Fareston (ProS-trakan, Bridgewater, NJ, U.S.A.), toremifene is approved for this indication worldwide, except in Canada. Preclinical data suggested that toremifene had a more favourable efficacy-to-toxicity ratio, but clinical data have not borne out that promise; the side-effect profiles are very similar. All of the toremifene studies included in the Cochrane review pre-dated the era of widespread first-line use of aromatase inhibitors (AIs) for metastatic breast cancer, and none of the patients involved would have received adjuvant AIs.

Toremifene has also been studied as adjuvant therapy for hormone receptor-positive breast cancer in postmenopausal women. In that setting, three large randomized trials comprising 3747 postmenopausal women demonstrated that toremifene and tamoxifen are equivalent in efficacy and safety⁴⁻⁶. However, despite those three trials, toremifene is not approved for that indication in any jurisdiction. Given the extensive clinical data supporting the use of AIs as adjuvant treatment in endocrine-responsive breast cancer in older women, toremifene is unlikely to gain widespread clinical traction in the adjuvant setting⁷. The use of SERMs in the management of postmenopausal breast cancer has declined in the past decade because of the general adoption of AIs, but SERMs continue to be clinically useful—especially for patients who cannot tolerate or who have a contraindication to AIs.

The options for premenopausal women are more limited. For those women, tamoxifen remains the only approved SERM available for the treatment of hormone receptor-positive breast cancer, because AIs are not effective in women with functioning ovaries. The publication of the ATLAS trial demonstrating the benefit of extending the duration of adjuvant tamoxifen to 10 years, may lead to renewed interest in SERMs in the adjuvant setting⁸. Seeing that no randomized trials are, at the present time, comparing toremifene with tamoxifen in premenopausal patients in the adjuvant setting, the data from the Qin series are of some interest. The authors report that toremifene could be used as adjuvant treatment in younger women, and within the limits of a retrospective study, the women appear to have derived clinical benefit comparable to that provided by tamoxifen.

The article does not provide level 1 evidence to support widespread use of toremifene in the adjuvant setting. Nevertheless, toremifene offers a viable option to patients and their physicians for situations in which, for some reason, neither tamoxifen nor an AI would be suitable. One such scenario might involve patients who require continued use of selective serotonin uptake

inhibitors to control severe depression or hot flashes. Tamoxifen is converted to its active metabolites by the *CYP2D6* gene, and because some selective serotonin uptake inhibitors are potent inhibitors of *CYP2D6* activity, their concurrent use may substantially compromise the efficacy of tamoxifen^{9,10}. In contrast, toremifene is primarily metabolized by *CYP3A4*, and *CYP2D6* is thought to play a minor role¹¹.

In summary, the retrospective Qin data are consistent with the conclusion that toremifene, like tamoxifen, is efficacious and safe to use in premenopausal patients with estrogen receptor–positive breast cancer. The data are consistent with randomized controlled trials in the published literature that demonstrate similar outcomes for the two agents in other clinical settings. Toremifene, while by no means the first-choice agent for adjuvant therapy of hormone receptor–positive breast cancer, might be a practical alternative in the real-world clinical setting, where patients requiring hormonal treatment for breast cancer cannot use either tamoxifen or AIS.

CONFLICT OF INTEREST DISCLOSURES

TS has acted as a consultant for Amgen.

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