

## EDITORIAL

# Long-term Adjuvant Tamoxifen Therapy and Decreases in Contralateral Breast Cancer

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**Tamoxifen** revolutionized personalized medicine as the first targeted therapy proven to save lives in cancer.<sup>1</sup> The paradigm change proposed to block the breast tumor estrogen receptor (ER), apply long-term adjuvant therapy to block estrogen-stimulated recurrences,<sup>1,2</sup> and apply the potential of

tamoxifen to prevent breast cancer.<sup>3</sup> These strategic recommendations were translated, during the past 3 decades, to clinical care.<sup>4</sup> A meta-analysis<sup>5</sup> of randomized clinical trials revealed that the strategic use of long-term adjuvant tamoxifen therapy is the key to therapeutic success. In addition, we now know that treating metastatic breast cancer (MBC) is only palliative at the end of life, but the same medicine saves lives if applied as long-term adjuvant therapy. Nevertheless, the question has to be asked whether the results would be the same outside the clinical trials process.

The report in this issue of *JAMA Oncology* by Gierach and coworkers<sup>6</sup> is reassuring because all the rules derived, until now, from randomized clinical trial overview analyses hold true.<sup>6</sup> The authors<sup>6</sup> performed a retrospective cohort study of contralateral breast cancer (CBC) in a population of 7541 patients from the records at Kaiser Permanente Northwest and Colorado from 1990 to 2008 and followed up through 2011. The median range of observation was 6.3 years, and 248 patients were identified to have developed CBC. Both tamoxifen and aromatase inhibitors reduced CBC, and longer adjuvant therapy proved to be more beneficial than shorter therapy. The authors<sup>6</sup> estimate that 4 or more years of adjuvant tamoxifen therapy will prevent 3 CBCs per 100 women by 10 years after first diagnosis of ER-positive breast cancer. The authors<sup>6</sup> stress that patients with breast cancer who are undergoing long-term adjuvant endocrine therapy should be encouraged to complete the full course. Indeed, this conclusion is even more important because in the future adjuvant endocrine therapy will last for 10 years.<sup>7-9</sup> However, the challenge is adherence. Simply stated, no medicine, no benefit. A previous report<sup>10</sup> calculates the number of deaths caused by nonadherence with adjuvant tamoxifen therapy. Low adherence results in early recurrence, increased medical costs, and a much worse quality of life.<sup>10</sup>

Gierach and coworkers<sup>6</sup> report the persistence of the protective effects of adjuvant tamoxifen after treatment stops on CBC risk and that this effect is dependent on the duration of tamoxifen therapy. The authors<sup>6</sup> cite a Danish study<sup>11</sup> that found that current users of tamoxifen had a reduced risk of CBC,<sup>11</sup> but former use of tamoxifen had no effect on CBC. Importantly,

the adjuvant therapy used was only for a short period (median, 1-2.5 years).<sup>11</sup> Persistence of the protective effects of tamoxifen using 5 years of treatment in high-risk populations is noted in the National Surgical Adjuvant Breast and Bowel Project trial<sup>12</sup> to reduce the risk of primary breast cancer in high-risk women. These data<sup>12</sup> are supported by the 96-month follow-up of the International Breast Cancer Intervention Study trial and the 20-year follow-up of the Royal Marsden Breast Cancer Prevention trial.<sup>13</sup> The rule is clear: long-term treatment with tamoxifen (5 years) produces a sustained beneficial effect in preventing breast cancer, whereas short-term therapy does not.

This clinical reality now presents the medical community with a paradox. Tamoxifen is a competitive inhibitor of estrogen action at the tumor ER. However, long-term adjuvant tamoxifen therapy<sup>1-3</sup> must be continuous because failure of tamoxifen to block the tumor ER will result in recurrence. However, this laboratory strategy<sup>3</sup> was not predictive for 5 years of adjuvant therapy. Patients survive without the benefit of tamoxifen blocking the ER to prevent recurrence. Herein lies the paradox. Tamoxifen is not cytotoxic, so where does the cytotoxicity of long-term tamoxifen therapy come from to protect patients after 5 years of adjuvant tamoxifen therapy?

The answer comes from laboratory research on the evolution of acquired resistance to tamoxifen.<sup>14-17</sup> Investigation of ER-positive breast tumors transplanted into tamoxifen-treated ovariectomized athymic mice results in the development of acquired resistance to tamoxifen within 1 to 2 years.<sup>12</sup> Uniquely, breast tumors develop because of tamoxifen treatment not despite tamoxifen treatment, and tumors use tamoxifen or estrogen to maintain tumor growth.<sup>14,17</sup> This biological knowledge is the scientific foundation for using an aromatase inhibitor (to prevent the postmenopausal patient from synthesizing estrogen) or fulvestrant (which destroys the tumor ER as a pure antiestrogen) as second-line therapies for MBC in which tamoxifen treatment has not worked. Antiestrogenic therapy is the strategy of choice because estrogen stimulates tamoxifen-resistant tumor growth.

Additional transplantation of ER-positive breast tumors with early acquired resistance to tamoxifen into tamoxifen-treated athymic mice for up to 5 years replicates the clinical strategy of 5 years of adjuvant therapy.<sup>11</sup> Tamoxifen-stimulated growth continues, but paradoxically physiologic estrogen has a significant antitumor effect.<sup>11</sup> Estrogen is cytotoxic, and tumors disappear completely. Yao and coworkers<sup>18</sup> proposed 2 clinical applications: (1) physiologic estrogen to treat MBC af-

# Long Term Tamoxifen Treatment For Breast Cancer

**ML Morrison**



## **Long Term Tamoxifen Treatment For Breast Cancer:**

## Whispering the Secrets of Language: An Emotional Quest through **Long Term Tamoxifen Treatment For Breast Cancer**

In a digitally-driven world where screens reign great and quick connection drowns out the subtleties of language, the profound secrets and mental nuances hidden within words often move unheard. Yet, nestled within the pages of **Long Term Tamoxifen Treatment For Breast Cancer** a interesting literary treasure pulsating with natural emotions, lies an exceptional journey waiting to be undertaken. Penned by a talented wordsmith, this marvelous opus encourages readers on an introspective journey, softly unraveling the veiled truths and profound influence resonating within ab muscles cloth of each and every word. Within the mental depths of this poignant evaluation, we will embark upon a sincere exploration of the book is core styles, dissect its captivating writing type, and succumb to the strong resonance it evokes serious within the recesses of readers hearts.

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