Integrative Cancer Therapies
2016, Vol. 15(3) 242–244

DOI: 10.1177/1534735416651329
ict.sagepub.com
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A Raloxifene Withdrawal Response: Translational Research, Definitions, and Clinical Applications

V. Craig Jordan, OBE, PhD, DSc, FMedSci[1]

Lemmo[1] contributes an interesting case report of a patient with estrogen receptor (ER) and progesterone receptor (PgR)–positive breast cancer, who was successfully treated, off label, with adjuvant raloxifene (60 mg daily) for 8 years until recurrence (ER/PgR-positive disease). This clinical case provides an unanticipated opportunity to revisit the biological rules of anti-estrogenic (aromatase inhibitors, tamoxifen and raloxifene) therapy, the manifestation of acquired resistance and the "withdrawal response." This is an important topic for the clinician. Breast cancer has the highest incidence of all cancers in women but the ER target has been the conduit for achieving the highest success in cancer therapeutics above all others.[2]

As a result, and to build upon success, it is important that efforts to integrate clinical observations with advances in understanding the mechanisms of acquired anti-hormone resistance, remain a priority to further aid patient survival.

The clinical use of the phrase "withdrawal response" was promoted through the 1950s and 1960s until the 1970s, to describe the paradoxical pharmacology of high-dose synthetic estrogen therapy, that is, diethylstilbestrol (DES), when used for the treatment of metastatic breast cancer (MBC), in women more than 5 years following their menopause.[3] Thirty percent response rates were routine, but when recurrent tumor growth resumed, withdrawal of the DES therapy caused a second tumor regression or a "withdrawal response." The synthetic estrogen was now fueling tumor growth. With the advance of tamoxifen in the 1970s,[4] which replaced high-dose DES therapy, clinicians again observed 30% response rates in MBA by blocking estrogen action. However, a "withdrawal response" was rarely observed (although one small series was published[5]). The reasons for this apparent failure with tamoxifen to produce a "withdrawal response," when it was commonly observed for DES with MBC patients titrated on and off treatment, was not that it did not exist, but instead the pharmacokinetics of tamoxifen were radically different than high-dose DES therapy, and the mechanism of acquired resistance was different.

High levels of tamoxifen and metabolites accumulate in the body and are retained for slow excretion over months after stopping treatment. By contrast, DES is completely excreted within days. Be that as it may, the actual explanation is far more complex when acquired resistance develops with tamoxifen. Laboratory studies with ER-positive breast cancers, retransplanted into tamoxifen treated animals for a decade, show several unique features not seen with any other cancer medicine.

Acquired resistance to tamoxifen develops under laboratory conditions in vivo within 2 years. This is consistent with the treatment of MBC. In the laboratory, breast tumors were discovered to grow because of tamoxifen treatment not despite tamoxifen treatment.[6,7] The reason that no "withdrawal response" is seen with tamoxifen when treatment is stopped is because tamoxifen remaining in the patient's body continues to stimulate tumor growth for many months. However, if this is the novel mechanism of acquired resistance to tamoxifen, seen clinically, the laboratory observation now created a conundrum: "If tamoxifen fails to control MBA and experimental tumors for no longer than 2 years, how is adjuvant tamoxifen able to control recurrence of breast cancer, with 5 years of treatment?"[8,9] The answer lies in the evolution of acquired resistance in cell populations, observed during the retransplantation into tamoxifen treated athymic mice for a decade.[10] The tamoxifen-treated tumors evolve their cell populations through selection pressure to expose a vulnerability, after 3 to 4 years: estrogen-induced apoptosis. Tumor regression occurs with physiologic levels of estrogen, after tamoxifen treatment is stopped.[11,12] Recent data with acquired anti-hormone resistant breast cancer cells in vitro illustrate how population can change within just a few months under

[1]University of Texas MD Anderson Cancer Center, Houston, Dallas/Ft Worth Living Legend Chair of Cancer Research, Houston, TX, USA

Corresponding Author:
V. Craig Jordan, OBE, PhD, DSc, FMedSci, Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, Dallas/Ft Worth Living Legend Chair of Cancer Research, 1515 Holcombe Boulevard, Unit 1354, Houston, TX USA.
Email: vcjordan@mdanderson.org

selection pressure. Cells with acquired anti-hormone resistance can change from aromatase and selective estrogen receptor modulator (SERM) resistant to become estrogen or SERM-stimulated,[13,14] just like the aythmic mouse model[6] and MBC.[5] Overall, this was thought to be a unique form of acquired resistance for tamoxifen, that is, tamoxifen-stimulated tumor growth, until the same form of acquired resistance, was found for raloxifene in both cell culture and athymic animal studies,[15,16] and now clinically in this case report.[1] Unlike tamoxifen, the polyhydroxylated raloxifene does not accumulate and is rapidly excreted within days. The "withdrawal response" following raloxifene-stimulated growth in the patient occurs because the medicine is excreted rapidly, to prevent growth but there is another cytotoxic component.

During the past 20 years, a hypothesis has emerged that a woman's own estrogen causes estrogen-induced apoptosis, following the cessation of long-term (5 years or more), adjuvant anti-hormone therapy.[10,11,17] This hypothesis, and supporting laboratory data,[11] provides a cytotoxic mechanism to explain the decreases in mortality after long-term tamoxifen is stopped.[8,9] What would be anticipated when the anti-estrogen tamoxifen was stopped, if estrogen-induced apoptosis of vulnerable cells did not occur, would be estrogen-stimulated recurrences, and death in patients once adjuvant therapy stops.

It seems to be a fact of cancer biology in patients that 5 years or more of estrogen deprivation is required to transform cell populations that initially grow with estrogen to become those that die with estrogen. Estrogen-deprivation can be achieved in many ways clinically: (*a*) 5 years after menopause is required for high-dose DES to treat MBC sucessfully[18]; or (*b*) 10 years after menopause, in the estrogen alone trial of the Women's Health Initiative, that produces a decrease in the incidence of breast cancer and an increase in survival from breast cancer[19]; or (*c*) the exhaustive treatment of MBC with anti-hormone therapies for over 5 years so that estrogen, now produces a 30% response rate[20,21] and does not produce growth. This clinical concept is replicated and supported by estrogen deprivation for breast cancer cells in culture,[22,23] and SERMs therapy (tamoxifen and raloxifene) for up to a decade observed in studies with aythmic mice.[15,16]

The large body of translational laboratory research, along with consistent clinical results, implicate long-term estrogen deprivation as the key to the subsequent cytocidal action of estrogen that has created a rule for cancer biology, which now is followed by the patient case report.[1] The postmenopausal patient received 8 years of adjuvant raloxfiene treatment prior to an ER/PgR-positive recurrence. The steady and persistent shrinkage in monitored hepatic metastasis mimic animal studies with estrogen-induced apoptosis, and supports the aforementioned clinical experience with estrogen in estrogen-deprived populations,[15,16] to produce the long-term decreases in CA-15-3 (figure 1 in the case report).[1]

We must thank Dr Lemmo for contributing an important new piece to the cancer biology puzzle of the "withdrawal response." This clinical observation further helps decipher the paradox of estrogen-induced apoptosis as a general principle to aid and enhance patient care.[24]

Acknowledgment

The author thanks the benefactors of the Dallas/Ft Worth Living Legend Chair of Cancer Research for their generous support.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article as a member of scientific advisory board for sermonix and stenogen.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Institutes of Health (NIH), MD Anderson's Cancer Center support grant CA016672 and Susan G. Komen for the Cure Foundation under award number SAC100009, and Cancer Prevention Research Institute of Texas (CPRIT) for the STARs and STARs Plus Awards.

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