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Editorial

Aromatase Inhibitors in Breast Cancer: The Legacy of Angela M. Hartley Brodie (1934-2017)

Balcer-Kubiczek E*
Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, USA

***Corresponding author:** Elizabeth K. Balcer-Kubiczek, Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, USA

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Editorial

Angela Brodie was an English-born and educated scientist who discovered, developed and introduced to cancer clinics a new class of targeted therapeutics called aromatase inhibitors that drastically reduce the biosynthesis of estrogens from their androgenic precursors. These medicines help primarily post-menopausal women – the group that is most susceptible to breast cancer – whose tumor cancers are likely to be responsive to anti-estrogen therapy [1]. Clinical benefits for these patients from treatments with an aromatase inhibitor include preventing or delaying recurrence after the treatment of the primary disease (surgery and/or radiation or chemotherapy), and lowering breast cancer risk in post-menopausal women who are at increased risk. Brodie's work on aromatase inhibitors spanned over more than four decades (1968-2016); it has been hailed as among the most important contributions to cancer cure.

According to the American Cancer Society 2017-2018 report [1] about 252,710 new cases of invasive breast cancer are expected to be diagnosed in the United States this year. Postmenopausal women aged 50 years or older at the time of diagnosis represent 209,000 (80%) of new cases (the average age of US women at the time of menopause is 51 years). There are four molecular subtypes of breast cancer that differ in terms of risk factors, clinical presentation, response to treatment, and outcomes; they are defined by the presence of absence of hormone (estrogen and/or progesterone) receptors (HR+/HR-) and levels of the human epidermal growth factor receptor 2 (HER2+/HER2-).

Approximately 60% of pre-menopausal and 75% post-menopausal breast cancers are HR+/HER2- and most of them express only the estrogen receptor. The development and growth of these tumors is driven by estrogen. Since its introduction into the clinic in 1971, tamoxifen -- an anti-estrogen that competes with estrogen for binding to the estrogen receptor -- has been the mainstay of therapy for hormone-receptor positive breast cancers. Around that time, Angela Brodie proposed an alternative strategy to block the synthesis of estrogen rather than to block the activation of estrogen receptors by estrogen. She reasoned that "there is no available anti-estrogen as good as no estrogen at all" (the statement attributed to Brodie [2]). It became her singular research goal to devise a clinically useful method of estrogen deprivation for treatment breast cancer. Brodie and her collaborators, notably her husband Harry Brodie, Craig Jordan (now at the University of Texas MD Anderson Cancer Center), Charles Coombes (now at the Imperial College of London), and Vincent Njar (at the University of Maryland School of Medicine) have focused on aromatase inhibitors as a potential site of blockage of estrogen synthesis.

Aromatase, encoded by the cytochrome P450 family 19 subfamily A member 1gene (CYPI9A1)on the chromosome 15, is the only enzyme in vertebrates that catalyzes a critical three-step process in which androgen (androstenedione and testosterone) is converted into estrogen (estrone and estradiol, respectively). Aromatase is expressed in many tissues, including fat, bones, muscles, skin, brain, liver, breast, placenta and ovaries. The activity (expression) of aromatase varies among different cell types depending on the cells' need for estrogen. Compared to the normal breast, breast cancer tissues over express CYPI9A1. The resulting increase in aromatase activity causes the observed build-up of estrogens, which enhance tumor-cell growth. Aromatase inhibitors are used primarily in post-menopausal women because the ovaries in pre-menopausal women produce too much aromatase for the inhibitors to block it effectively. Conversion of androgens, produced by the adrenal glands, is the main source of estrogen after cessation of ovarian function in postmenopausal women.

In 1974 Richard Santen (the University Of Virginia School Of Medicine) reported reversible suppression of aromatase activity in post-menapausal women by aminoglutethimine, now considered the first generation aromatase inhibitor. The drug (the trade name Cytadren) has been used since the 1960s for treatment of epilepsy, hyperthyroidism and Cushing's disease, but was not approved as an aromatase inhibitor in the US due to poor specificity and selectivity. Between 1973 and 1977 Angela and Harry Brodie identified the second generation aromatase inhibitors, 4-hydroxyandrostenedione (4-OHA) and its derivative 4-hydroxy-4-androstene-3, 17-dione (formestane; the trade name Lentaron) [3].

In the late 1970s Brodie's subsequent pre-clinical studies in a rat mammary breast carcinoma model compared 4-OHA to tamoxifen and confirmed 4-OHA as the first molecule selectively targeting aromatase in breast cancer cells without disrupting estrogen signaling in other tissues [3]. Her laboratory results presented at a Rome conference in 1980 attracted enough attention to initiate in 1984 comparative trials of 4-OHA against tamoxifen in breast cancer patients at Royal Marsden Hospital by Charles Coombes. The Coombes data provided the first proof of concept in the clinic of the anticipated differences in the estrogen-related effects hypothesized and validated in the Brodie laboratory [4]. Although initially approved in Europe and Japan for treatment in estrogen-dependent postmenopausal breast cancer, formestane was withdrawn due to poor oral bioavailability and discovery of third generation oral aromatase inhibitors.

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The third generation aromatase inhibitors currently approved by the Food and Drug Administration (FDA)in the US are anastrozole (the trade name Arimidex) and letrozole (the trade name Femera), both of which temporarily inactivate aromatase by preventing binding androgen to the enzyme, and exemestane (the trade name Aromasin) which permanently inactivates aromatase by binding to the substrate-binding site of aromatase. Chronologically, exemestane, a derivative of formestane developed by di Salle and Lombardi at Pharma (then Farmitalia Carlo Erba) was the first compound to enter preclinical development in 1986. The aromatase inhibitor programs in Novartis (then Ciba-Geigy) and AstraZeneca led to the development of, respectively, letrozole in 1990 and anastrole in 1994.

From mid-1990s onwards, a series of clinical trials of the third generation aromatase inhibitors showed clinical superiority to tamoxifen as judged by the endpoints of disease-free survival, recurrence and incidence of contralateral invasive breast cancer. The overall side-effect profile was markedly better for these drugs than tamoxifen. Clinical data confirmed the theoretical expectation from the Brodie's hypothesis that the greater estrogen suppression would increase the clinical efficacy. However, currently available aromatase inhibitors are not without problems. Nearly total estrogen deprivation (in the order of 95%) has been associated with bone loss, a significant problem in post-menapausal women who are already subjected to bone loss. In addition, low levels of estrogen remaining (in the order of 5%) may lead to drug resistance, another undesired outcome in some women whose disease worsen during the treatment or after initial positive response. Overcoming acquired resistance is the next big challenge for aromatase research.

Efforts through the 2000s to develop better aromatase inhibitors were handicapped by the lack of an experimental structure of this unique enzyme. The year 2009 marked the publication of the crystal structure of aromatase by Ghosh and colleagues at the State University of New York Upstate Medical University [5]. The discovery of the real atomic model has reinvigorated the field of aromatase research from perspectives of understanding of the mechanisms of action and structure-guided drug design. Since 2009, more than hundred next-generation aromatase inhibitors have been developed, including azole and quinolone derivatives, flavone analogs, coumarins and tamoxifen metabolites (summarized in table 3 in ref. 6). The promising candidates identified by virtual in silico screening have progressed to an in vitro testing in cellular model systems [6].

The year 2017 marked the 20th anniversary of the introduction of letrozole in the United States and worldwide. It is quite rare to be involved in the development of a drug that successfully completes the journey from discovery to approval and then advances to care in a therapeutic field. Angela Brodie had such an opportunity. Reflecting on the future directions of hormone therapy for breast cancer, she wrote in 2007: "Because of the importance of estrogen as a stimulus to the development and progression of breast cancer, estrogen synthesis (via aromatase) and action (via estrogen receptor) continues to be exceptional targets for the treatment and chemoprevention of breast cancer. Thirty years ago the idea of targeting and blocking estrogen action to treat breast cancer with tamoxifen or the idea of blocking the estrogen synthetase (aromatase) enzyme appeared to be a simple and straightforward concept. Today, these simple approaches have become multifaceted with many layers of complexity that are being explored to enhance tissue selectively, address intrinsic resistance and block the development of acquired anti-hormonal resistance" [7].

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