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EDITORIALS

Deep Time: The Long and the Short of Adjuvant Endocrine Therapy for Breast Cancer

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"Deep time"—a phrase popularized by science writers such as John McPhee and Stephen J. Gould—refers to the intellectual challenge of grappling with the vast geologic and cosmologic time scale, a problem that has constrained geologists for centuries, because it is so hard to conceptualize events transpiring over billions of years. Oncologists, a group usually confronted by the pressing demands of the here and now, have a variation on the deep time problem when they contemplate management of hormone receptor–positive, early-stage breast cancer, a disease with a long natural history and subtle, fascinating intrinsic variations. Adjuvant endocrine therapies often span years, creating a long-trajectory of treatment, adverse event management, and surveillance and thus differ in deep time from some other oncology outcomes measured in short-term response rates or progression intervals of months.

Recent reports have yielded important insights into the deep time issues of adjuvant endocrine therapy. The Early Breast Cancer Trialists' Collaborative Group reiterated the long-term value of 5 years of tamoxifen, which lowers breast cancer recurrence and death through 15 years of follow-up.[1] The Early Breast Cancer Trialists' Collaborative Group shows a clear time-dependence effect for tamoxifen; the annualized risk of recurrence is greatest in years 0 through 4 (3%–4% risk per year), but so are benefits of tamoxifen (relative risk reductions, 42%–53%). Yet late recurrence remains an important issue in adjuvant therapy. In years 5 through 9, there is a persistent 2% to 3% annual recurrence risk, which has been lowered by tamoxifen (relative risk reduction, 32%). After 10 years, the annual risk of recurrence is approximately 2%, and there is no lingering risk reduction on a year-to-year basis for having received tamoxifen for the initial 5 years.

Long-term results are now available from several of the canonical adjuvant trials of aromatase inhibitors, including the Intergroup Exemestane Study (IES) reported by Bliss et al,[2] which randomly assigned patients to either ongoing tamoxifen or a switch to exemestane after 2 years of tamoxifen. As with the tamoxifen overview experience, the long-term follow-up in the IES trial shows a residual annual event rate of 3% to 4% that extends outward for at least another 5 years after the end of 5 years of adjuvant endocrine therapy, regardless of whether the patient received tamoxifen or tamoxifen followed by an aromatase inhibitor (AI). Recurrences after the conclusion of drug treatment far outnumber those that arise during treatment. Similar findings with regard to late recurrence risk have been reported from the ATAC and BIG 1-98 trials, which compared tamoxifen versus an AI for a total of 5 years of therapy.[3,4] In both the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial and Breast International Group trial 1-98 (BIG 1-98), the annual recurrence risk in years 6 through 10 was approximately 2% per year, and half of all recurrences arose in these later years of follow-up. Collectively, these findings underscore the persistent risk of late recurrence in estrogen receptor (ER) –positive breast cancer and the relative inability of 5 years of endocrine therapy to mitigate that risk. This pattern of persistent risk stands in marked contrast to ER-negative breast cancers, in which the recurrence risk tails off dramatically beyond the 5-year benchmark.

Predictors of early recurrence of ER-positive breast cancer among women receiving endocrine therapy include larger tumor stage and positive nodal status, lower levels of hormone-receptor expression, higher grade and proliferative markers, human epidermal growth factor receptor 2 overexpression, and high recurrence scores on multigene arrays.[5-8] Not coincidentally, these are clinical factors that are likely to confer benefit from adjuvant chemotherapy. By contrast, predictors of late recurrence are not well characterized, although nodal involvement and lobular histology are associated with greater risk of relapse after 5 years of endocrine therapy[9-11] It is tautological to state that women at jeopardy for late recurrence are those who do not experience early recurrence. Thus, it is likely that biologic predictors of late recurrence would be the converse of markers of early recurrence, but to date, there has been little exploration of biomarkers or gene profiles associated with later events. Ideally, clinicians would like to identify which tumors pose persistent peril such that they warrant ongoing, longer durations of adjuvant endocrine therapy and, by contrast, which tumors might adequately be treated with shorter durations so patients need only 5 years of therapy. At present, there are no clinical markers sufficiently reliable to determine whether duration should vary from patient to patient. Undoubtedly, the answer will lie in a combination of risk defined both by baseline stage and by pathobiologic features associated with treatment benefit and inherent propensity to recur.

A criticism of the switching studies of AIs, in which women received tamoxifen first and were then randomly assigned to treatment with or without AIs is that they are biased against patients who experience early relapse before the switch. However, this critique does

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not apply to the Austrian Breast and Colorectal Cancer Study Group trial 8 (ABCSG 8), which enrolled women at the time of initial diagnosis to treatment with either tamoxifen for 5 years or to tamoxifen followed by an AI for a total of 5 years. Long-term updates from ABCSG 8 confirm the favorable prognosis for these patients and show minimal difference between tamoxifen and the AI.[12] This observation differs from the long-term findings in the IES trial[2] and the switching experience in the BIG 1-98 study,[13] a likely consequence of an important feature of ABCSG 8—the inclusion of lower risk patients with breast cancer with lower-grade tumors. Such patients have a better overall prognosis, making it more difficult to document gains in outcome.

A puzzling observation in previous reports of adjuvant therapy with AIs was the lack of a significant survival advantage compared with patients treated with tamoxifen. The similar observed survival rates were likely a consequence of the limited follow-up for a long-term disease, the contribution of locoregional or contralateral breast cancer events to study end points, the incidence of interval, non–breast cancer deaths among postmenopausal women, and the relatively modest differences in efficacy between AIs and tamoxifen. Another factor seems to have been crossover from tamoxifen to AI treatments. After reports of benefit for AI treatments, a large group of women originally allocated to receive tamoxifen alone started taking AIs. Novel statistical approaches attempt to account for selective patient crossover in the analyses of AI effectiveness. In the NCIC MA.17 study (Letrozole After Tamoxifen in Treating Women With Breast Cancer), in which women who had completed 5 years of tamoxifen treatment were randomly assigned to treatment with an AI or placebo, nearly two thirds of all patients crossed over from placebo to an AI at an average time point of 2.7 years after randomization or somewhere between years 7 and 8 years after diagnosis.[14] With adjustment for that high rate of crossover, the MA.17 study suggests a survival advantage for use of an AI instead of tamoxifen alone. A similar adjustment of BIG 1-98 also disclosed a survival advantage for patients given AIs instead of tamoxifen alone.[15] Thus, late crossover from tamoxifen to an AI further confounds the survival end points in these adjuvant studies when analyzed on an intent-to-treat basis.

An intriguing corollary of the cross-over analyses is the implication that late crossover from tamoxifen to AI therapy must be highly effective treatment, sufficiently potent to negate the survival advantages of earlier use of an AI.[16] This begs the question: in the current era, with aromatase inhibitors accepted as a standard component of adjuvant therapy, would either longer total durations of AI therapy beyond 5 years or extended courses of treatment involving sequences of tamoxifen and AIs for longer than 5 years be superior to 5 years of an AI given up front? Current guidelines from the American Society of Clinical Oncology recommend that postmenopausal women "consider incorporating AI therapy at some point during adjuvant treatment, either as up-front therapy or as sequential treatment after tamoxifen," limit total AI exposure to 5 years and acknowledge that the "optimal timing and duration of endocrine treatment remain unresolved."[17(p3784)] Alas, we have still not answered the pressing questions of sequence and duration. Several clinical trials are seeking to define the appropriate duration of adjuvant aromatase inhibition, and those data are awaited eagerly.

The long-term follow-up data in the articles that accompany this editorial and elsewhere[2-4,12,14] testify to the long arc of hormone receptor–positive breast cancer, confirm the enduring overall safety of tamoxifen and AIs, and provide reassurance that the well-characterized major adverse events of therapy either stabilize or resolve with cessation of treatment. The substantial near-term successes of adjuvant chemotherapy and endocrine therapy have shifted both the natural history and the dialogue in ER-positive, early-stage breast cancer for oncologists and patients alike. The issue of late recurrence—deep time for clinicians and survivors—has emerged as a fundamental challenge. RCTs have shown equivalence for either 5 years of AI treatment or a sequenced regimen of tamoxifen followed by an AI for a total of 5 years.[13,18] For women who receive AI-based adjuvant treatment, it remains unclear whether a longer program of extended therapy with an AI beyond 5 years of initial adjuvant treatment will outperform a shorter 5-year course of adjuvant endocrine therapy. Progress in the deep time problem of early-stage breast cancer will depend on answering the long and the short of that question.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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