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Editorial

EDITORIAL

Extended Adjuvant Endocrine Therapy for Postmenopausal Women: Treating Many to Benefit a Few

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Over the last decade, a number of phase III multinational randomized clinical trials (RCTs) have evaluated the benefit of extending adjuvant endocrine therapy with an aromatase inhibitor (AI) in postmenopausal patients. These trials have varied in their design with respect to the type (tamoxifen, AIs, or both) and duration (two to 10 years) of initial adjuvant endocrine therapy, the duration of extended AI therapy (2.5 to 6 years), and the total length of therapy with an AI (three to 10 years). These differences have complicated the interpretation of the findings. Overall, these trials have demonstrated that extended adjuvant endocrine therapy is associated with a modest 2% to 4% reduction in absolute risk of recurrence (1–8). Much of this benefit has been on locoregional recurrence and new primary, with only about a 1% to 3% reduction in risk of distant metastasis (1–8). Only one study, MA.17, has demonstrated an improvement in overall survival, but just in patients with node–positive disease (1).

The modest benefit of extended adjuvant endocrine therapy documented in large clinical trials suggests that this treatment is active in a small subset of patients. The conundrum has been how to best define this group. Given this scenario, understanding safety and tolerance to treatment and developing and implementing precision medicine tools are critical steps for improving treatment recommendations. Goldvaser and colleagues (9) present compelling data focusing on the safety of extended adjuvant endocrine therapy for postmenopausal patients. The meta-analysis, which included 16 349 patients, combined hierarchically collected aggregate-level data reported in each primary RCT. Among patients receiving prolonged therapy with an AI, there was a statistically significant but small increase in odds of cardiovascular events, with an absolute weighted pooled difference of 0.8%, number needed to harm (NNH) of 122 patients; bone fractures, with an absolute weighted pooled difference of 1.4%, NNH of 72; and rate of discontinuation for adverse events, with an absolute weighted pooled difference of 4.8%, NNH of 21. There was no statistically significant association between risk of death without breast cancer recurrence and use of prolonged AIs. To reduce subjectivity, two independent reviewers extracted the data from each RCT. Data were appropriately controlled for aggregated median age at random assignment, duration of follow-up, and prior use of tamoxifen or AIs, none of which influenced these differences. An open question remains if a median follow-up of 30 to 82 months from included RCTs would be long enough to capture relevant cardiology-related outcomes.

A few potential limitations of this study exist. First, cancer recurrence is a clinically significant cause of morbidity (10) that should not be minimized. While this study is focused on the risks of extended adjuvant endocrine therapy with AIs, from a practical perspective, these risks are always balanced against the potential benefits of the therapy. Second, the increase in severe adverse events presented here was relatively low, but could have been underestimated. The harmful events evaluated in this meta-analysis were not the main outcome of the RCTs, patients were removed from the trials at disease progression, compliance to extended adjuvant AI could be lower than expected, time to harmful event would likely vary according to the type of adverse event, and the nature and clinical significance of harmful events, particularly cardiovascular, varied. Because this study combined only aggregate-level data reported in each primary RCT, meta-regression exploring the adverse events rate according to duration of follow-up per treatment arm was not possible. It would be conceivable that survivorship bias could interfere with rate estimation of rare adverse events. Third, initial adjuvant endocrine therapy with an AI prior to enrollment to one of the selected RCTs varied from none to up to

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six years of treatment and could influence the likelihood of adverse events. Fourth, although the main trials on this subject are in the public domain, the literature search was restricted to English only and did not include databases such as EMBASE or CENTRAL (11). And fifth, the current report has not evaluated the potential impact of extended AI therapy on quality of life and other adverse events from AIs, such as arthralgias, hot flashes, vaginal dryness, and other sexual side effects.

It is recognized that a substantial number of patients develop breast cancer recurrence regardless of extended adjuvant endocrine therapy, while many others are considered for this treatment strategy without need. Therefore, the development of diagnostic tools to help identify patients who will benefit from this therapy, to identify those who will do well regardless and thus should be spared the needless toxicities and cost, and finally to select those with dormant-resistant disease for alternate investigational therapies is the next critical step in this field. Unfortunately, the detection or prediction of cancer dormancy remains a clinical challenge (12). Because microscopic foci of cancer cannot be detected by current scanning technology and invisible disease cannot be biopsied, current efforts are focusing on two main strategies: 1) understanding the molecular characteristics of the tumor or of systemic fluids collected at initial diagnosis and/or 2) examining the biologic fluids sampled at the end of initial adjuvant endocrine therapy (ie, circulating tumor cells (13), cell-free DNA in plasma assays looking at somatic genomic alterations (14), single nucleotide polymorphisms, and copy number variations) (15). A number of assays, including PAM50 risk of recurrence score (16), Breast Cancer Index (17,18), EndoPredict (19), Oncotype DX (20), and IHC4 score (21), are examples of biomarker assays aiming to help identify patients who are at a higher risk for recurrence by evaluating their baseline characteristics. The disadvantage of this approach is the potential clonal evolution of cancer, leading to the emergence of new clones that were not detectable at diagnosis. On the other hand, mathematical models are under development in an attempt to predict which tumor has the potential to undergo aggressive clonal evolution (22,23). However, at present, the existing assays have not been sufficiently validated to be utilized routinely in clinic, a statement supported by recent American Society of Clinical Oncology guidelines (24).

And finally, after a long period without groundbreaking changes in initial adjuvant endocrine treatment, ongoing clinical trials have the potential to change the landscape, including those evaluating CDK4/6 inhibition and mTOR inhibitors combined with endocrine therapy (NCT03078751, NCT02513394, NCT03081234, NCT01674140).

Goldvaser and colleagues (9) are to be commended for providing clear estimates of the serious risks of extended endocrine therapy with an AI utilizing the best available evidence. In the clinic, these risks need to be balanced against the benefits of this therapy. As a critical next step, we need well-validated molecular predictive tools to help personalize decisions regarding adjuvant endocrine treatment for postmenopausal women with hormone receptor–positive breast cancer.

Notes

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