EDITORIAL

New Stars in the Sky of Treatment for Early Breast Cancer

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Since Sir George Beatson observed in 1896 that breast tumors in premenopausal women sometimes regressed after oophorectomy,[1] numerous investigations have established that estrogen stimulates the growth of breast-cancer cells. Three newer strategies reduce the growth-stimulating signals of estrogen: interfering with the binding of estrogen to its receptor, the primary mode of action of the antiestrogen agent tamoxifen in premenopausal and postmenopausal women; decreasing the estrogen levels in the blood and the tumor, the mechanism of action of aromatase inhibitors in postmenopausal women; and destroying the estrogen receptor, which is how the drug fulvestrant exerts its antitumor activity.

During the course of the clinical development of these antiestrogen strategies, we have learned four major lessons. First, they work only in hormone-receptor–positive tumors, which account for two thirds of breast cancers. Second, cross-resistance can be circumvented in advanced disease (e.g., tamoxifen-resistant tumors are generally not resistant to aromatase inhibitors). Third, as adjuvant treatment, tamoxifen has had unprecedented success in reducing breast-cancer–related mortality worldwide. Finally, tamoxifen, and probably the other agents, can prevent breast cancer.[2]

Information concerning untoward side effects of these endocrine therapies is solid only with regard to tamoxifen, as indicated by the Oxford Overview, which has analyzed, among other topics, the adjuvant use of this drug in more than 30,000 women, some of whom have been followed for 15 years.[3] It is clear that tamoxifen is associated with a small risk of thromboembolic disease and endometrial cancer and that this risk increases with the duration of treatment. The drug has positive effects, however, on bone mineral density and blood lipid profiles. These divergent effects of tamoxifen, which are caused by its estrogen-agonist activity in certain tissues, weaken its therapeutic index to some extent.

There is intense interest in the molecular mechanisms of endocrine resistance in general and in resistance to tamoxifen in particular. Growth factors, cellular stress, and other cellular pathways that signal directly to the estrogen receptor and some of its key regulators are prominent in mediating resistance; this process can modulate the estrogen receptor in a way that causes the activity of tamoxifen to switch from an antagonist to an agonist effect.[4]

The current knowledge regarding resistance to tamoxifen provides a sound molecular basis for the impressive results of the large and well-conducted adjuvant trial reported by Coombes and colleagues in this issue of the *Journal*.[5] The study involves postmenopausal women who had undergone excision of primary breast cancer and were then treated with tamoxifen for two to three years before randomization. At the time of the second planned interim analysis of this trial, the group of women who had been assigned to switch to the aromatase inactivator exemestane had significantly longer disease-free survival than women who continued to receive tamoxifen. The total planned duration of both the sequential and the standard adjuvant endocrine therapy was five years.

This observation is not a surprise to the medical oncology community. There is considerable evidence that aromatase inhibition is superior to other endocrine manipulations in postmenopausal women with tamoxifen-resistant advanced breast cancer. Moreover, aromatase inhibitors are superior to tamoxifen as first-line endocrine therapy for metastatic disease and as neoadjuvant (preoperative) treatment.[6]

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Exemestane, an irreversible steroidal inhibitor that inactivates the enzyme aromatase, thereby blocking the conversion of androgens to estrogens in peripheral tissues, is effective in women whose breast cancer has progressed despite therapy with both tamoxifen and anastrozole or letrozole, which are competitive, reversible, nonsteroidal aromatase inhibitors. Exemestane is also superior to megestrol acetate, in terms of survival, in women in whom disease has progressed despite tamoxifen therapy, and it may also be superior to tamoxifen for advanced disease.[7]

The strengths of the study by Coombes et al. include its adequate statistical power, the fact that it involved multiple groups of investigators in 37 countries, its independent management, its double-blind treatment comparison, its acceptable ineligibility and dropout rates, its efficacy analysis according to the intention-to-treat principle, and the consistency of the treatment effect among all clinically relevant subgroups. The weaknesses of the study are the immaturity of the data in terms of overall survival and safety and the lack of information on estrogen-receptor status for 17 percent of the participants. As we progressively leave the era of empirical medicine and enter one of molecular medicine, it is becoming essential to secure tumor-tissue collection in trials of adjuvant agents, for the purpose of translational research. Such research is important because analysis of the expression profiles of breast-cancer genes has shown striking differences between tumors that express estrogen receptors and those that do not. The method has also identified at least three subgroups of estrogen-receptor–positive tumors with distinct molecular signatures; in addition to different prognoses, these subgroups may have different responses to endocrine treatments.[8]

Will the study show a survival benefit with longer follow-up? The answer is uncertain. The hazards of death could be disproportionate over time; moreover, endocrine therapy profoundly affects the rates of contralateral breast cancer and local relapses, for which curative treatment exists. However, in the present trial, the risk that an early crossover masks a survival benefit is small, given that more than 90 percent of the participants had completed their randomly assigned therapy at the time the report was written. This attribute represents a sharp contrast with another important trial of adjuvant therapy, by Goss et al., involving letrozole.[9] In that placebo-controlled trial, which showed an early benefit of extended adjuvant therapy with letrozole after five years of tamoxifen treatment, less than 1 percent of the participating women had completed their randomly assigned therapy when the study-group assignments were revealed. When the first results of the Anastrozole, Tamoxifen Alone or in Combination (ATAC) trial were released, none of the participants had completed their assigned therapy.[10]

The results of these three trials at a median follow-up of only 30 months does not allow us to conduct a useful risk–benefit analysis, which is an integral part of making appropriate treatment decisions. Although the short-term toxic effects of aromatase inhibitors have not been particularly worrisome[5,9,10] and clear advantages over tamoxifen in terms of thromboembolic and uterine complications have emerged,[10] the long-term consequences of estrogen deprivation in postmenopausal women remain a concern. Particular attention will need to be paid to bone and cardiovascular health, cognitive and sexual function, and quality of life. It will also be important to see whether, with longer follow-up, the suggested reduction in the incidence of second, nonbreast cancers associated with exemestane treatment is a real phenomenon.

Considering these three important trials, what should clinicians do? Many more years will be required to fine-tune the risk–benefit assessment of adjuvant aromatase inhibitors, but the use of these agents should be discussed with patients who are suitable candidates, and they should be informed about the limitations of the current data. In my opinion, women whose risk of recurrence is high are reasonable candidates for the inclusion of an aromatase inhibitor in plans for adjuvant treatment, whereas women with a low risk of recurrence might give more weight to long-term safety and be better served by tamoxifen therapy.

Women and their physicians are now confronted with difficult choices, and clinical investigators suddenly realize that the acceleration of the conduct of trials of adjuvant therapy can create problems, particularly in the case of early reporting: the National Surgical Adjuvant Breast and Bowel Project B33 trial, the sister of the trial reported by Goss et al. in which exemestane was used instead of letrozole for extended adjuvant therapy, was "killed" by the publication of the letrozole study; the Arimidex–Nolvadex (ARNO) study and the Breast International Group 01-98 trial, which are exploring sequences of tamoxifen with anastrozole and letrozole, respectively, might be in danger as well.

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The breast-cancer research community must rethink the rules for the early reporting of results from trials of adjuvant therapy. These rules must be amended to reflect a better tradeoff between the desire to inform women and society rapidly about a more effective therapy for a potentially lethal disease and the need to collect solid data on the safety of the therapy.

Although some advocate that results be disclosed early for reasons of safety only or after some preset minimal follow-up period,[11] a more realistic approach is to base early disclosure on significant differences between the rates of distant relapse. Indeed, treating such relapses may prolong lives but does not save lives. Since distant relapses accounted for roughly half the events that triggered early reporting in the three trials of adjuvant aromatase inhibitors, perhaps the use of stopping rules based on distant-disease–free survival could have provided an extra year of follow-up before reporting. This proposal will be put on the agenda of the Breast International Group[12] and, if deemed appropriate, will be discussed with its closest partner, the North American Breast Intergroup.

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