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Introduction

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Improved understanding of the processes underlying the development and persistence of invasive breast cancer has led to significant advances in the treatment of this unfortunately common disease. Although metastatic breast cancer is still a terminal disease, most cases of early breast cancer are now associated with an extended disease-free interval. If treated adequately, most women with primary breast cancer can expect to survive, suggesting that early intervention with surgery, radiotherapy and systemic therapy may be curative in many cases.

Complete tumor resection is essential for the local control of primary breast cancer, and to prevent or reduce metastatic spread. Neoadjuvant treatment can be given to render inoperable tumors resectable, or to cause operable tumors to regress, thereby reducing the extent of surgery.[1] Locoregional radiotherapy is used after surgery to reduce the incidence of local recurrence. To reduce distant and locoregional recurrence, systemic adjuvant therapy is used. Systemic adjuvant therapy may consist of chemotherapy, endocrine therapy or both, depending on disease and patient characteristics. Endocrine therapy is effective only in hormone-receptor-positive (HR+) disease, whereas chemotherapy can be used regardless of hormone receptor status.[2]

Tamoxifen has been the mainstay of adjuvant endocrine therapy for several decades, and successfully reduces the incidence of recurrence, contralateral breast cancer and death among postmenopausal women with HR+ early breast cancer. However, prolonged exposure to tamoxifen is associated with a gradual change in the risk:benefit ratio, which becomes unfavorable after about 5 years.[2,3] Recently, an alternative endocrine agent, the aromatase inhibitor (AI), letrozole, has become available to further protect against breast cancer recurrence and death in women who remain disease-free after 5 years of tamoxifen.[4,5]

The third-generation AIs, letrozole, anastrozole and exemestane, are generally well tolerated and have now been shown to be more effective than tamoxifen in preventing disease recurrence in the adjuvant setting. On the basis of these data, the discussion is turning to whether these agents should displace tamoxifen as the gold standard adjuvant endocrine treatment in postmenopausal women.

Through different mechanisms of action, tamoxifen and AIs deprive HR+ tumor cells of the growth-promoting effects of estrogen. In postmenopausal women, peripheral (non-ovarian) aromatase activity is the sole source of circulating estrogen, and the third-generation AIs have been shown to achieve almost complete inhibition of aromatase activity, profoundly reducing circulating estrogen levels. In contrast, tamoxifen does not influence circulating estrogen levels but binds to the estrogen receptor, operating as an antagonist in breast cancer cells and most other tissues, but also as a partial agonist in tissues including bone, the urogenital

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tract and cardiac tissue. Thus, AIs and tamoxifen can have opposing effects in some estrogen-responsive tissues, particularly bone.

The first-generation AI, aminoglutethimide, was shown to have efficacy in relapsed, advanced breast cancer, but poor tolerability, reflecting the low selectivity for aromatase, prevented widespread use. To improve tolerability, AIs with greater selectivity for aromatase were developed: two second-generation AIs (fadrozole and formestane) and the three third-generation compounds now in clinical use (anastrozole, letrozole and exemestane). The third-generation AIs can be divided into two classes; steroidal and non-steroidal, based on their chemical structure. Exemestane is a steroidal AI, which competes with the natural substrate for aromatase and binds irreversibly to the enzyme at the active site. Anastrozole and letrozole are non-steroidal AIs that bind reversibly to the enzyme at the cytochrome P450 moiety.[6] It is not known whether these different mechanisms of inhibition are clinically relevant; however, in the advanced disease setting, responses have been observed by switching between a non-steroidal AI and a steroidal AI.[7]

The third-generation AIs are up to 10,000 times more potent than aminoglutethimide,[6] and have been investigated in the early and advanced breast cancer settings. In this supplement, data are reviewed from clinical trials using anastrozole, letrozole and exemestane in HR+ breast cancer, which have led to their use at all stages of breast cancer treatment. Particular attention is paid to recent studies in the adjuvant setting, in which AIs have been shown to be more effective than tamoxifen in preventing breast cancer recurrence and have demonstrated at least equivalent tolerability. The results of these trials prompted the American Society for Clinical Oncology,[8] the St. Gallen International Expert Consensus on Primary Therapy of Early Breast Cancer[9] and the National Comprehensive Cancer Network[10] to update international guidelines in 2005 to recommend that an AI is used as adjuvant endocrine therapy for HR+ early breast cancer, either instead of tamoxifen or in a sequence after tamoxifen.

Recent data from large, randomized trials comparing AIs with tamoxifen in the early adjuvant setting are discussed by Professor Mouridsen. The different treatment strategies that have been studied are described, and the limitations of the trials are discussed. On the basis of data from these trials, in which AIs were consistently shown to be more effective than tamoxifen, AIs are now gradually displacing tamoxifen as the adjuvant therapy of choice in HR+ disease. Professor Goss continues the discussion of the efficacy of AIs in early breast cancer with his review of the MA.17 extended adjuvant trial, in which letrozole became the first agent to be shown to confer a significant benefit in women who remained disease free on completion of 5 years of tamoxifen therapy.

The efficacy of the third-generation AIs as an adjuvant strategy is not in question, but long-term tolerability is important when treating a disease in which women have good prospects for long-term survival. Dr. Perez discusses the long-term safety of AI use in the third article in this supplement. The relative risks and benefits associated with AIs and tamoxifen are covered in detail, concluding that AIs are associated with predictable and manageable side effects, and, arguably, have a better tolerability profile than tamoxifen.

The articles included in this supplement, which are based on presentations from the satellite symposium 'The quiet revolution in breast cancer treatment: how aromatase inhibitors are displacing tamoxifen' at ECCO 13, aim to further disseminate the efficacy and tolerability findings from trials of third-generation AIs in HR+ breast cancer. The long-term tolerability of these agents, which could influence the widespread acceptance of these drugs, is discussed, as well as the question of whether the individual third-generation AIs are clinically equivalent. The third-generation AIs have the potential to improve outcomes for millions of women with HR+ breast cancer and, through further research, our understanding of how best to use these highly effective agents will increase, enabling patients to gain maximum benefit from adjuvant endocrine therapy.

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