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Chemoprevention in High Risk Women

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Abstract

A number of second-line metastatic breast cancer trials have been conducted comparing the progestational agent, megesterol acetate, and a third-generation aromatase inhibitor following failure. At a minimum, these selective aromatase inhibitors demonstrated equivalent if not superior efficacy to megesterol acetate in patients with resistant advanced metastatic breast cancer as a second-line therapy, thus paving the way for direct head-to-head comparisons with the established first-line hormonal agent.

Keywords: Efficacy; Hormone; Treatment; Inhibitor; Stabilization; Progression

Introduction

Anastrozole was the first of the selective third-generation aromatase inhibitors to be compared directly with tamoxifen. Two large randomized Phase III trials, the North American Trial conducted in the US and Canada, and Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability, conducted in Europe, Australia, New Zealand, South Africa, and South America were conducted to compare tamoxifen and anastrozole as a first-line therapy for metastatic breast cancer with respect to time to disease progression, objective response rate, and tolerability [1]. These trials were prospectively designed for a combined analysis. Anastrozole demonstrated equivalence in comparison with tamoxifen in terms of median time to disease progression, objective response rate, and clinical benefit rate, defined as objective response rate and stabilization of disease for weeks. In contrast, in the US trial there was a statistically insignificant improvement in objective response rate in favor of anastrozole. However, a significant improvement in median time to disease progression was shown for treatment with anastrozole of months in comparison with months for tamoxifen treatment. In addition, the clinical benefit rate was significantly higher with anastrozole compared with tamoxifen. It is important to note that, while these trials were prospectively designed with the idea of a combined analysis, there was considerable patient heterogeneity in terms of hormone receptor status between the trials. Specifically, within TARGET, up to participants had unknown hormone receptor status. In comparison, only participants in the US trial had unknown hormone receptor status [2]. It is well recognized that tumors expressing hormone receptors derive significant benefit from hormonal therapy,in contrast, hormone receptor-negative tumors are not impacted significantly by the addition of hormonal therapy. Including a number of patients with uncertain hormonal status in these studies may have diluted a differential effect by the hormonal agent. The combined analysis for the US and TARGET studies suggested that anastrozole daily was comparable with tamoxifen. In a retrospective subgroup analysis, women with known hormone receptor-positive disease had a longer time to disease progression when treated with anastrozole in comparison with tamoxifen-treated patients. In terms of tumour response, the objective response rate was for anastrozole treated women and for tamoxifen. The clinical benefit rate also favored anastrozole in comparison with for tamoxifen treatment. Letrozole has also been compared against tamoxifen in the first-line setting for metastatic breast cancer by the International Letrozole Breast Cancer Group. This study evaluated patients from November until January and elicited more favorable results in patients treated with letrozole [3]. At a median follow-up of months, women treated with letrozole had a 3-month improvement in time to progression when compared with tamoxifen, as well as a better objective response rate and longer time to treatment failure. Women treated with letrozole were also found to have a longer time to chemotherapy, with a median of 16 months, suggesting that it may provide patients with a better quality of life than tamoxifen, which delayed chemotherapy by months. No statistically significant benefit in overall survival could be demonstrated with letrozole treatment, although this was numerically prolonged for the women initially randomized to letrozole [4]. Women on this study were allowed to cross over, and approximately women in each arm did transition to the opposite drug, perhaps diluting a survival signal. Exemestane has also been compared with tamoxifen in postmenopausal women with metastatic breast cancer. Patients were assigned to receive daily oral treatment with either exemestane or tamoxifen. Women treated with exemestane did have an early progression-free survival advantage which diminished over time to in comparison with for tamoxifen treated women at months. This translated into a statistically insignificant difference in the two progression-free survival curves by the log rank test and Kaplan–Meier analysis. In addition, no advantage was identified. However, tumor response rates were higher for exemestane, with an objective response rate of compared with for tamoxifen treated women, and fewer exemestane treated women had evidence of disease progression at months of follow-up in comparison with tamoxifen treated women [5]. The optimal sequence of hormonal therapy for women with advanced breast cancer remains ill-defined. However, selective aromatase inhibitors have been identified by the NCCN as preferred first-line therapy for postmenopausal women who have received prior antiestrogen therapy, are within year of antiestrogen exposure, antiestrogen naïve, or greater than year out from prior antiestrogen therapy [6]. Women who have had progression of disease on a nonsteroidal aromatase inhibitor may respond to a steroidal aromatase inhibitor and vice versa, although responses in this setting are modest. Adjuvant treatment Five years of treatment with the selective estrogen receptor modulator, tamoxifen, for many years

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considered the gold standard, has been shown to reduce annual breast cancer recurrence rates by almost one half and breast cancer mortality by nearly one-third. Aromatase inhibitors have now been demonstrated to improve efficacy in numerous large randomized trials compared with tamoxifen in post-menopausal women, given alone in the adjuvant setting as monotherapy for years, sequential therapy sequenced with tamoxifen, or as extended therapy following years of tamoxifen treatment. The publication of new data over the past led the American Society of Clinical Oncology to issue an update to the clinical practice guidelines, which identified major trials using aromatase Despite new data, recent recommendations were not significantly different from prior guidelines recommending an aromatase inhibitor as either primary, sequential, or extended adjuvant treatment to reduce the risk of breast cancer recurrence compared with tamoxifen alone in postmenopausal women [7]. Deciding when to incorporate an aromatase inhibitor and for how long remains less clear. We will review emerging data supportive of multiple potential strategies on which to base a clinical decision. Two large trials have compared an aromatase inhibitor with tamoxifen as initial therapy for early breast cancer. Both have released updated analyses showing an improved relapse-free survival advantage for the aromatase inhibitor as initial adjuvant therapy, and suggest that its use initially may be important to reduce early events in patients at high risk for early recurrence [8]. The trial, first reported, was the first large randomized trial to demonstrate a possible advantage of an aromatase inhibitor over tamoxifen in the adjuvant setting. This large, double-blind, double-placebo, three-arm trial compared treatment with anastrozole, tamoxifen, or both drugs in combination for years in over women. The combination group was halted after the first analysis because it showed no improvement in efficacy over tamoxifen mono-therapy. In the ATAC trial, participants were documented hormone receptor-positive. An improved disease-free survival was not observed in hormone-receptor negative patients, confirming that only patients with hormone receptor-positive tumours benefit from endocrine therapy. In the previously mentioned meta-analysis conducted, no differences in terms of cerebrovascular events, death without recurrence, or second cancers were identified [9]. There was a trend towards increased death without recurrence in the women treated with upfront aromatase inhibitor therapy as opposed to those who were initially treated with tamoxifen and then switched to an aromatase inhibitor. This suggests two potential hypotheses; firstly, a possible negative impact associated with duration of aromatase inhibitor treatment and, secondly, a potential mitigating effect of upfront tamoxifen. Rates of hypercholesterolemia or dyslipidemia have been increased with aromatase inhibitors in most trials, but not all. Impaired lipid metabolism could serve as a mechanism for enhancing cardiovascular disease as a result of treatment with aromatase inhibitors. In the trial, evaluation of aromatase inhibitor therapy can be made in comparison with placebo. However, all women were initially treated with tamoxifen for years which may have potentially imparted a positive impact on cardiovascular health. In this study, after a median follow-up, no significant differences were noted for the development of hypertension or hypercholesterolemia. In women over the age of years, rates of cardiac disease were increased, but this did not differ by treatment arm. Interestingly, in a single institution report, postmenopausal women to be treated with letrozole were prospectively followed and monitored for total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein, triglycerides, and estradiol at base line and at months of treatment. In this study, there was a non-significant increase in total cholesterol and low-density lipoprotein which reverted back to baseline at the 12-month mark. Triglycerides were elevated and remained elevated throughout the period, but the increase was considered non-significant [10]. Estradiol levels were significantly suppressed at 3 months and remained suppressed throughout. Thus, the effect of aromatase inhibitors on cardiovascular health remains a contentious issue. The results of the MA-17 trial indicate no significant decrement in the cardiovascular parameters monitored in comparison with placebo. The increased risk in comparison with tamoxifen as suggested by the two meta-analyses may be more a reflection of a mild cardio-protective effect offered by tamoxifen as opposed to a negative impact imparted by aromatase inhibitors. Until these issues are more clearly defined, close monitoring of patients with pre-existing cardiac disease is likely warranted. Tamoxifen has been the standard of care for women with hormone receptor-positive breast cancer for the past several decades. Large, randomized, controlled trials conducted in the past two decades have consistently shown an advantage of aromatase inhibitors over tamoxifen for both advanced and early stage breast cancer in postmenopausal women. There continues to be questions regarding the optimal sequencing of hormonal agents.

Conclusion

New data are emerging comparing aromatase inhibitors and evaluating their side effect profiles more closely. Choice of hormonal therapy must ultimately be determined based on recurrence risk, individual tolerance, bone health, and the overall side effect profile.

Acknowledgement

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Conflict of Interest

None

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