A decade for hope: Extending aromatase inhibitor adjuvant therapy

“It is also good to ask questions when you know that they will not have answer. Because behind them you can add others as idle as the first, as impertinent, as capable of comfort in the return of the silence that will receive”.

José Saramago. Las maletas del viajero. 1986

The use of adjuvant endocrine therapy in breast cancer with positive estrogen receptors (ER+) has evolved rapidly in recent decades. Starting from the use of tamoxifen as the only therapy available, through combinations with suppression of ovarian function in premenopausal patients, the use of aromatase inhibitors (AI) sequentially in patients post-menopausal or premenopausal with concomitant ovarian suppression, to 10-year extension tamoxifen therapy in all patients, regardless of ovarian function.

In July 2016, in The New England Journal of Medicine, a study evaluating the use of aromatase inhibitors for five years after the use of tamoxifen alone or with sequential AI, as adjuvant endocrine therapy in patients with ER+ breast cancer is published. If the use of tamoxifen was found to have a positive impact on reducing mortality and recurrence with five years of therapy, was consistent also to evaluate IA.

In the MA.17 study, 1,918 postmenopausal patients who were randomly assigned to receive letrozole (959 patients) or placebo (959 patients) for an additional five years to adjuvant endocrine therapy with tamoxifen followed by AI were evaluated. Only 21% of patients included in this study did not receive adjuvant endocrine therapy with tamoxifen, but with AI only. All patients included were disease-free the time of study entry. In the letrozole group, 55 patients (5.7%) had local or distant recurrence and 13 patients (1.4%) had contralateral breast cancer. In the placebo group, 68 patients (7.1%) had recurrence and 31 patients (3.2%) had contralateral breast cancer. The rate of 5-years disease-free survival for the AI group was 95% (95% CI, 93 to 96) and 91% (95% CI, 89 to 93) in the placebo group. A HR: 0.66 to disease recurrence or occurrence of contralateral disease was obtained when comparing both groups (95% CI, 0.48 to 0.91, p = 0.01), i.e., a 34% reduction using letrozole. By including in the analysis deaths from breast cancer, the result was very similar.

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because the patients who died from the disease were the same that had recurrence or occurrence in the contralateral breast.

Overall survival at five years was similar between the two groups: 93% in the letrozole group and 94% in the placebo group. The causes of death were breast cancer, other primary cancers and cardiovascular events. In the prespecified subgroup analysis, there was no difference in overall survival. The annual incidence of contralateral breast cancer was of 0.21% in the letrozole group and 0.49% in the placebo group (95% CI, 0.10 to 0.32, p = 0.007) with a HR of 0.42, ie, a very interesting reduction of risk of contralateral breast cancer of 58%.

With regard to side effects, there were significantly more patients who developed osteoporosis and presented fractures in the letrozole group (p = 0.001); there was no difference in relation to other side effects. The use of bone-protecting therapies was similar in both groups, which did not involve a bias in the study.

Based on these results, the authors conclude that the use of AI for five additional years in postmenopausal patients with ER + breast cancer is safe and beneficial, with little impact on quality of life and adequate side effect profile. The benefits include decreased recurrences of the disease, with a significant increase in disease-free survival, and a decreased incidence of contralateral breast cancer, without registering an improvement in overall survival.

Although the MA-R17 study can not be compared to the ATLAS study, because in the latter the use of tamoxifen for 10 years in pre- and post-menopausal patients was evaluated and only used this drug as adjuvant endocrine therapy, it seems that regarding the side effects, extended use of AI seems to have a better profile. In an analysis in this portal on the publication of ATLAS study, because tamoxifen has been associated with increased endometrial cancer and pulmonary embolism, as more serious side effects, its use is restricted in patients with risk factors for these pathologies. Prolonged use of AI has as main side effect the development of osteoporosis, a condition that can be prevented and treated. However, its use is limited to post-menopausal patients, such as those included in this study because in younger patients, probably the extent of ovarian suppression for 10 years is not possible and would benefit most from the use of tamoxifen extended form, provided they do not have comorbidities that contraindicate the use of this drug. Similarly, menopausal patients with contraindications to the use of AI, such as arthritis or osteoporosis, probably would benefit more from extended therapy tamoxifen therapy IA.

After the evidence of extended tamoxifen for five years shown in the ATLAS study and now with the MA.17R study also prefaced with letrozole for five years, offer to provide many patients with breast cancer expands, individualizing each case the long breath use of adjuvant therapy with a decreased disease recurrence. Maintaining a therapeutic measure in breast cancer for a decade, more than a mere extension in time, it is emerging as an interesting change in the perception of the disease. With ten years of adjuvant endocrine therapy, in some way we would be treated breast cancer as a chronic condition, but it would be a novel form of tertiary prevention too. Something unthinkable a few years ago.

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