DOI - 10.37951/CEREM-V2I1-36-37

REVIEW ARTICLE

ADVANCES IN ADJUVANT SYSTEMIC THERAPY FOR EARLY BREAST CANCER: 'ESCALATION' OR 'DE-ESCALATION'

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ABSTRACT

This article focuses on 'escalation' or 'de-escalation' in early breast cancer scenario. In other words, identifying areas where optimal care may be achieved with 'less' or 'more' treatment. The needs of a specific patient may be better defined through consideration of subset analyses or other individualized approaches to care. Adjuvant therapies for the patient nowadays imply that the treatments need to be adjusted to the patient's tumor characteristics, co-morbidities, economic constraints and acceptance of available therapies.

KEYWORDS: ADJUVANT TREATMENT; BREAST CANCER; ESCALATION; DE-ESCALATION.

INTRODUCTION

The use of systemic adjuvant therapy, along with the progress in surgery, radiation therapy and early diagnosis, improved the prognosis of patients with early breast cancer. With the discovery of new therapeutic targets, some protocols were reformulated and became more intense and/or lasting, more toxic and also more expensive. Examples of escalation in practice in our country are:

1 - The use of dense dose chemotherapy regimens (AC regimen - doxorubicin and cyclophosphamide - 4 cycles every 14 days with granulocyte growth factor support instead of every 21 days) which results in a reduced risk of relapse at 10 years and cancer-specific mortality even for hormone-positive tumors[1];

2 - The use of adjuvant capecitabine for 6 months for triple-negative tumors that did not reach a complete pathological response after neoadjuvant chemotherapy, based on the Asian study CREATE-X. This study demonstrated a gain in disease-free survival and overall survival of the experimental arm compared to placebo[2];

3 - The use of dual HER-2 blockade with trastuzumab and pertuzumab in neoadjuvancy and/or adjuvancy, especially for tumors larger than 2 cm and/or with a compromised armpit. It is worth noting that, in adjuvancy, the results for double block were modestly better for disease-free survival compared to trastuzumab alone. Long-term follow-up shows greater benefit for those with positive lymph nodes. [3,4];

4 - The use of extended endocrine therapy, that is, beyond the 5 years of standard therapy, reaching 10 years of anti-hormone therapy; this strategy has not yet demonstrated a gain in overall survival, only disease-free survival, especially for patients at high risk of recurrence [5,6,7];

5 - The performance of ovarian blockade (permanent or temporary) for premenopausal patients based on the results of the SOFT and TEXT studies updated in 2018, showed gain of recurrence-free survival and overall survival for high-risk patients with indication for chemotherapy[8,9];

6 - The use of platinum (mainly carboplatin) for patients undergoing neoadjuvant chemotherapy, which results in an increased probability of a complete pathological response regardless of the presence of a mutation in the BRCA1/2 genes. It must be considered the need for dose adjustments and treatment interruptions due to toxicity, in most cases hematological[10,11].

At the same time that more patients are being cured due to improvements in the therapeutic arsenal, a considerable portion of them are being exposed to treatments with potential toxicities in the short and long term without a justifiable clinical benefit. The main challenge is to pro-

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perly select the true low-risk patients and thus offer less intense therapies, with less sequelae and also with less costs. The most important examples of current de-escalation in systemic therapy are:

1 - The isolated use of paclitaxel weekly for 3 months and trastuzumab for 1 year for HER2-positive breast cancer patients, with less than 3 cm (especially less than 2 cm and with positive hormone receptors). The phase II APT trial, updated in 2017, showed a recurrence-free survival of 93.3% in 7 years with this scheme [12,13];

2 - The omission of adjuvant anthracyclines, highly effective drugs for the treatment of breast cancer but with a not insignificant risk of heart failure and leukemia. In HER2 negative patients, at least 2 studies and a meta-analysis showed similar efficacy of the docetaxel and cyclophosphamide protocol for 6 cycles compared to the anthracyclic and taxane-based regimen mainly for patients with negative lymph nodes [14,15,16]. In HER2-positive patients, the use of the TCH protocol (docetaxel, carboplatin and trastuzumab) showed similar efficacy and less cardiac toxicity compared to the anthracycline regime. The same was observed in neoadjuvance when the TCH scheme with pertuzumab (TCHP) was compared to the schemes with anthracyclines[17].

3 - The use of genetic signatures for patients with initial tumors, smaller than 5 cm, positive hormone receptors and HER-2 negative in order to avoid the use of adjuvant chemotherapy. The most requested in Brazil are Oncotype Dx and Mammaprint. Such tools classify the tumor in different categories according to the likelihood of recurrence, saving low-risk patients from chemotherapy [18-21].

Studies point to a possible therapeutic equivalence between the use of 6 months and 12 months of adjuvant trastuzumab. However, the publication of data from the PHARE and PERSEPHONE studies, as they are divergent, did not lead to a change in global practice in relation to the current 12-month treatment [22.23].

CONCLUSION

Despite the complexity in understanding the various variables that permeate the treatment of breast cancer, efforts continue so that more and more patients increase their chances of cure and receive treatments proportional to their risk of recurrence, avoiding unnecessary toxicities without compromising the effectiveness of the treatment.

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