

TAILORED MANAGEMENT OF ADVANCED BREAST CANCER: IS IT WORTH TO TAKE A BIOPSY OF METASTATIC SITES?

22nd International Congress on Anti Cancer Treatment

CONTE PierFranco, PIACENTINI Federico

Dept. of Oncology, Hematology and Respiratory Diseases – Modena University Hospital

Breast cancer is a clinically and molecularly heterogeneous disease. The molecular classification represents the foundation of treatment selection for early and advanced breast cancer: endocrine manipulation and/or HER2 targeted agents are administered on the basis of oestrogen and progesteron receptors and HER2 expression. In routine clinical practice, the assessment of these predictive parameters (ER, PR and HER2) is usually carried out in the primary tumor, and these results are also used to guide treatment choice in metastatic disease, even if it occurred many years after the primary diagnosis.

However, the appropriateness of this approach can now be questioned for some reasons. First of all, several reports have been published showing a lack of concordance in the expression of HER2 and hormonal receptors between primary tumors and disease recurrence, with range of discordance between 0% and 34% and between 18% and 54% respectively. According to the literature data, we have observed in a retrospective study of 75 patients an overall disagreement of 16% in the HER2 status (ten patients changed from negative to positive, two cases only from positive to negative) and of 21% in the expression of hormonal receptors (nine cases changed from positive to negative and seven cases from negative to positive) from primary tumors to disease recurrences. Noteworthy, it has recently been reported that also PI3KCA mutation occurs with high frequency but differently in primary and metastatic breast cancer (PIK3CA mutation was detected in 45% of the primary tumors and in 53% of paired metastases).

The increasing use in the adjuvant setting of targeted agents might exert selective pressure, possibly facilitating a modification in tumor phenotype: in fact, the change from a positive to negative hormonal receptor or HER2 status might reflect acquired resistance to hormonal or anti-HER2 therapy. But the finding that receptor status can change to both directions not support the hypothesis that during tumor progression, de-differentiation always occurs leading to a more aggressive phenotype. At the same time the conversion from a negative to positive phenotype can offer the patient the opportunity to receive a treatment that possibly could ameliorate the outcome: this issue has obviously direct relevance for treatment decision-making. Furthermore, new imaging and radiological techniques (e.g., ultrasound or computed tomography-guided biopsy) have improved our ability to easily and safely obtain tissue samples from metastatic sites.

The mechanisms underlying the change in the expression of hormonal receptors and HER2 have yet to be completely understood. According to intratumoral heterogeneity theory a clone with metastatic potential could not be detected in the primary lesion and could form metastatic deposits with different biologic properties. Another way is

a possible genetic drift or a clonal selection which occurs during tumor progression or a selective pressure of prior therapies (as mentioned above).

Finally the technical reproducibility of the ER, PR and HER2 assay could in part justify the rates of discordance, because immunohistochemistry or FISH have less than 100% of accuracy and reproducibility. Several studies indicate that even when consecutive slides from the same tumor block are stained in different laboratories or interpreted by different pathologists, significant levels of discordance rates are found; differences in fixation methods, choice of antibody and threshold levels can also have a profound effect on immunohistochemistry results.

In summary, a substantial rate of discordance in pathology and molecular markers between primary breast cancer and asynchronous metastases is possible and can alter the patient management in up to 20% of them. Tissue confirmation should be considered standard of care in patients with clinical and/or radiological suspicion of metastatic recurrence and lesions amenable to biopsy with minimal invasiveness.

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