



Emerging new predictive biomarkers in metastatic breast cancer: Caveolin-1 and weekly nab-paclitaxel plus gemcitabine, are we on for tomorrow?

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Despite the considerable progresses and the high efficacy of adjuvant medical treatments (chemotherapy, hormonotherapy and targeted therapy) in early breast cancer, up to a third of breast cancer patients still recur and die (1). As breast cancer comprehends a large spectrum of different tumor phenotypes, some with a more indolent behavior and others, more aggressive, with a poor short-term outcome, a major clinical issue has arisen as how to handle patients with metastatic disease.

Currently, treatment selection at the time of diagnosis of metastatic breast cancer (mBC) is based on several clinical variables, including interval from diagnosis and treatment for localized disease, adjuvant therapy already used, tumor burden and the presence of a symptomatic disease.

The genomic “revolution” has revealed the genomic structure, function and evolution of breast cancer heterogeneity (2,3). However, how this great amount of data translates into clinical scenario is often not clear, and definition of the intrinsic disease phenotype is yet limited to some immunohistochemical techniques, which allow to differentiate three major groups of mBC, with obvious therapeutic implications: the hormone receptor positive group [which expresses the estrogen receptor (ER) and/or the progesterone receptor (PgR)], the human epidermal growth factor receptor 2 (HER2) positive group [which expresses HER2 by immunohistochemistry (IHC), or amplification detected by fluorescence in-situ hybridization

(FISH)] and the “triple negative” group, which is negative for ER, PgR, and HER2.

For patients candidates to chemotherapy, namely for those with a hormone receptor positive disease who progressed after hormonal therapy and for those with a triple negative breast cancer, there is no consensus standard of care for chemotherapy regimens in mBC.

However, the eternal debate between the use of a combination chemotherapy or sequential single agent chemotherapy in the management of mBC patients, has found in recent years a consensus (4,5). It has been agreed that sequential monotherapy should be recommended as the preferred choice for mBC, and combination chemotherapy be reserved for selected patients with high tumor burden, rapid clinical progression, life-threatening visceral metastases or need for rapid symptom and disease control (4,5).

These indications are only partially useful, as it remains the issue of the choice between different drugs, with only a few direct comparisons available. New prognostic and predictive markers of efficacy would, therefore, be very helpful, in order to distinguish between patients who need more aggressive treatments from those who could be reasonably treated by sequential monotherapy and to select drugs according to the greatest likelihood of efficacy, avoiding unnecessary toxicities.

Zhao *et al.* recently published a prospective, single arm, phase 2 trial in *BMC Cancer* that fits into this old debate,

offering new interesting food for thought (6). The trial was designed to assess the efficacy and safety profile of the combination of weekly nab-paclitaxel plus gemcitabine in mBC Chinese patients. Nab-paclitaxel was approved by the US Food and Drug Administration in 2005 for the treatment of mBC patients. It is an albumin-bound, 130-nm-particle formulation of paclitaxel (Abraxane[®]) that was developed to improve the efficacy of taxanes, limiting the risk of side effects due to the solvents used to formulate paclitaxel and docetaxel (7). The results obtained by Zhao *et al.* in a cohort of 84, rather heterogeneous, mBC patients indicated that the aforementioned combination had a clinically significant antitumor activity with a manageable safety profile (6). An objective response rate (ORR) of 52.4% (complete response 2.4% and partial response 50%) was reported, with a median progression-free survival (PFS) of 7.9 (95% CI: 6.6–9.2) months and a median overall survival (OS) of 25.8 (95% CI: 20.4–31.1) months (6).

Median PFS and OS were significantly longer in patients who received the combination as first-line treatment, as compared with those who received the combination as second-line therapy or more [hazard ratio (HR) for PFS, 2.2; 95% CI: 1.3–3.6; median OS, not reached for first-line; second-line or more, 14.9 months; Log-rank P=0.000] (6). The toxicity profile was manageable. The incidence of grade 3–4 neutropenia was 45.2%. Six patients (7.1%) experienced grade 3 neurotoxicity, which caused dose reduction or discontinuation. Noteworthy, the authors report 20.2% of all grade thrombocytopenia and only 8.3% of grade 3–4 (6). Exploratory study included immunohistochemical detection of tumor/stromal Caveolin-1 (Cav-1) to investigate its putative role as a predictive biomarker for the efficacy of the combination of weekly nab-paclitaxel and gemcitabine (6).

Although interesting, these results have some limitations. The study is a single-arm trial with no control group. Moreover, it tested a combination chemotherapy that has already been evaluated in the past (8) and it involved a relatively small number of patients with heterogeneous disease characteristics and therapeutic setting. The inclusion in the trial of patients with different tumors phenotypes (luminal, 72.6%; triple-negative, 14.3%; HER2 positive, 11.9%), different tumor burden (visceral disease, 82.1% *vs.* non-visceral, 17.9%) and at different times in the natural history of the disease (70.2% at first line of chemotherapy *vs.* 29.7% at second line or more) has the advantage of representing an “unselected” cohort of mBC patients as might be expected in the real clinical practice (6). On the other hand, it makes data difficult to

compare. Conversely, it's a fact that the therapeutic strategy of mBC is going towards personalization of therapies, mainly based on molecular characteristics of the disease. In designing clinical trials, it's our duty to ask ourselves how the results will fit into the current strategy and how they will represent a scientific evolution. For example, we cannot forget the progresses made in delineating a well-defined therapeutic sequence in HER2 positive mBC, with no place for combination chemotherapy (4). In addition, the latest most exciting advances in this field have been made in well-selected patient populations (i.e., PARP inhibitors in BRCA-mutated patients, anti-PD-L1 monoclonal antibodies in triple negative PD-L1-positive tumors, PI3K inhibitors in PIK3CA-mutated cancers) (9–11).

The study of Zhao *et al.* has the merit of proposing an interesting exploratory analysis including immunohistochemical detection of tumor/stromal Cav-1, to investigate its role as a predictive biomarker for the efficacy of the combination of weekly nab-paclitaxel and gemcitabine (6).

Cav-1 is an integral component of plasma membranes that forms the major structural constituent of caveolae (flask-shaped invaginations of plasma membrane), which are found at the cell surface in most cell types (12). Increasing amount of data shows that Cav-1 is expressed in many mesenchymal cells, such as adipocytes, fibroblasts and endothelial cells (13). The “genesis” of human cancer, ultimately due to genomic instability, encompasses a broad spectrum of different processes. During tumor growth, cancer cells develop the potential to leave behind the link with contiguous normal tissues. Moreover, self-renewal, alteration of the cell cycle, avoidance of apoptosis and unlimited replication are others attributes of cancer cells (14). Within a growing tumor mass, phenotype changes of cancer cells comprehend the capacity to promote angiogenesis, infiltrate neighboring tissues and metastasize to distant organs. Increasing evidence shows that Cav-1 plays a pivotal role in gaining most of these hallmarks of cancer cells and can induce tumor invasion and metastasis by a process of epithelial-mesenchymal transition, which allows epithelial tumor cells to develop invasive and metastatic capabilities (15). Moreover, a large amount of data converges in correlating the development of the neoplastic phenotype with quantitative and qualitative changes in the protein composition of the extracellular matrix, underscoring the important role played by the microenvironment in tumor growth (16).

The principal way of nab-paclitaxel transport appears to be through receptor-mediated transcytosis, which

is mediated by Cav-1 (17). Supposing that tumor and stromal Cav-1 expression may be a biomarker of nab-paclitaxel efficacy, through IHC the authors evaluated Cav-1 expression of breast cancer tissue (staining intensity and percentage of cells and deriving an H-score) and stromal tissue (staining intensity) (6). Formalin fixed paraffin-embedded (FFPE) tissue was requested from all enrolled patients, but only 45 of 84 patients were available for FFPE tissue. Higher tumor Cav-1 level significantly correlated with a longer PFS of nab-paclitaxel and gemcitabine (Log-rank $P=0.03$), while significant a longer PFS was detected in patients with lower stromal Cav-1 level (Log-rank $P=0.047$), defining a subgroup of patients with high tumor but low stromal Cav-1 staining who had the longest PFS, with a median PFS of 10.1 months (95% CI: 2.4–19.1) (6). However, no significant correlation was detected between tumor/stromal Cav-1 expression and OS and ORR (6). These results suggest that Cav-1 might play a different biological role, depending on its compartmentalization. This differential effect has been confirmed in other studies, even if its prognostic value is not clear-cut (12,13,18). What appears to be the most interesting aspect, from the point of view of practical implications, is the predictive value of the Cav-1 IHC signature referred to the efficacy of weekly nab-paclitaxel and gemcitabine, as these results suggest that it may be possible to identify distinct mBC phenotypes that are characterized by different sensitivity to treatment (6). In this sense, it is certainly intriguing that the supposed mechanism of action of Cav-1 and its central role in receptor-mediated transcytosis of nab-paclitaxel perfectly fits with these preliminary data, since the longest PFS detected in patients with high tumor but low stromal Cav-1 staining suggests that the optimal uptake of nab-paclitaxel in breast cancer cells, while reducing competitive dispersion of the drug in stromal cells and tissue, results in better treatment efficacy (6).

However, these findings should be regarded as merely exploratory, namely in reference to the small number of cases, and, as such, they should be evaluated with caution. As aforementioned, the study is a single-arm trial with no control group. Indeed, in the absence of a control arm, it is impossible to define the predictive or rather prognostic value of a biomarker. In this regard, we have to stress that Cav-1 expression has already been associated to specific breast cancer phenotypes but, in the present study, the limited number of cases prevented a specific analysis by subgroups (6,19). Nonetheless, these results justify IHC methodological standardization and prospective validation

in larger series of Cav-1 as a predictive biomarker of weekly nab-paclitaxel and gemcitabine efficacy.

Despite of huge amount of data and knowledge acquired on breast cancer biomarkers during last decade, several challenges still need to be overcome, in order to transfer the progress achieved into clinical practice. First of all, understanding on cancer signaling should encourage the identification of new molecular prognostic tools that are likely to improve patients risk stratification, which is essential in treatments selection. Secondly, in the era of tailored medicine, more translational research is required in order to identify biomarkers that could help to predict drug response and resistance. Lastly, for the development of biomarkers to be used in routine, beyond the prognostic and/or predictive value, technical reproducibility and standardization, cost and clinical validation are essential aspects to consider.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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