Predictors of response to neoadjuvant chemotherapy: Importance of breast cancer subtypes

Sir,
Preoperative systemic therapy in locally advanced breast cancer (LABC) has many benefits and has become widely used in the present times. The study by Bansal et al.\(^\text{[1]}\) was a welcome addition to our knowledge. A wide range of factors predicting response to neoadjuvant chemotherapy (NACT) in LABC have been identified, but the quest remains inconclusive. In this regard, we would like to emphasize some important aspects.

Breast carcinoma as an entity is comprised of molecularly distinct diseases. It is natural that these entities would have different predictors of resistance to chemotherapy. A recently published study, de Ronde et al.\(^\text{[2]}\) analyzed this and found that for human epidermal receptor (HER) +ve, estrogen receptor – ve breast cancer, subtype specific predictor based on clinical features outperformed the generic, nonspecific predictor. They advocated that both specific and generic predictors should be evaluated when attempting to predict treatment response in breast cancer. It primarily would depend on the specific type of predictor being evaluated.

The molecular predictors evaluated by Bansal et al.\(^\text{[1]}\) that is, carcinoembryonic antigen related cell adhesion molecules, carcinoembryonic antigen-related cell adhesion molecule 5, 6 (CEACAM 5, 6) and SLC7A5 have been used as predictors of therapy in breast cancer earlier. CEACAM 6 has also been used to predict breast cancer recurrence to endocrine therapy. In a study, Maraga et al.\(^\text{[3]}\) retrospectively tested whether significantly up-regulated CEACAM 6 on immunohistochemistry specimens was predictive of breast cancer resistance to tamoxifen therapy on long term follow-up. The results were indicative of significantly more CEACAM 6 expression in the relapsed group of patients as compared to nonrelapsed control, supporting an important role of CEACAM 6 in endocrine resistant breast cancers. Similarly, SLC7A5 has also been implicated in endocrine resistance in breast cancers. Mihaly et al.\(^\text{[4]}\) in a meta-analysis to validate predictors to tamoxifen resistance identified SLC7A5 as one of the most promising genes along with two other genes.

Tsang et al.\(^\text{[5]}\) evaluated CEACAM 6 expression in two independent cohorts of invasive breast cancer patients, and CEACAM 6 expression was found in 37.1% of invasive cancers. It was significantly positively correlated with HER two expression especially the HER overexpressed subtype. In this subtype, it was associated with high nodal stage patient outcome.

Thus, it needs to be prioritized that expression of these three molecular predictors be correlated with receptor/ molecular subtypes of breast cancer to know their exact significance as a predictor of response to neoadjuvant therapy in carcinoma breast. It would have been highly appreciable to know the correlations of the molecular markers with breast cancer subtypes in the study done by Bansal et al.\(^\text{[1]}\) The molecular markers CEACAM 6 and SLC7A5 have been proven as markers of endocrine

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1. Bansal et al. (2014)
2. de Ronde et al. (2015)
3. Maraga et al. (2016)
4. Mihaly et al. (2017)
5. Tsang et al. (2018)
Letters to the Editor

Sir,

Currently, skeletal related events (SREs) include pathologic fractures, spinal cord compression, hypercalcemia, and severe bone pain is common with multiple myeloma, breast, prostate and lung malignancy. SREs are treated with bisphosphonates (BPs) widely, and 1–18% patients have been reported with osteonecrosis that is called as BPs related osteonecrosis of the jaw (BRONJ).

Except BPs other recently reported pharmacological agents associated with osteonecrosis of the jaw (ONJ) are denosumab and bevacizumab. The antiangiogenic effects of BPs are of particular interest in regard to ONJ, due to the importance of neo-vascularization in wound healing. Dental extraction, bone invasive surgeries and mucosal trauma are risk factors for ONJ, healing after which requires the revascularization. It is possible that the interruption of the normal healing process increases the risk for ONJ. Angiogenesis and ONJ have also been linked by the case reports of ONJ occurring in patients treated with antitumor therapies targeting vascular endothelial growth factor (VEGF). Guarneri et al. provided an excellent presentation of the ONJ in patients treated with bevacizumab or sunitinib and the rationale for performing their analysis of bevacizumab in patients with locally recurrent or metastatic breast cancer (MBC).

Vascular endothelial growth factor A is a potent proangiogenic growth factor that stimulates the proliferation, migration, and survival of endothelial cells. VEGF-A is one of the important proteins that is also expressed by tumor cells and is an important target of anticancer therapy. Bevacizumab is a humanized anti-VEGF-A monoclonal IgG1 antibody (molecular weight, 149 kDa).

In combination with chemotherapy, it is approved for the treatment of advanced colorectal cancer, advanced nonsmall cell lung cancer, MBC and advanced renal cell cancer. As a single agent, it can be used for second-line treatment of advanced glioblastoma multiforme. Further studies are being conducted in other solid tumors as well, indicative of the potential therapeutic benefit of bevacizumab in combination anticancer therapy.

The overall incidence of ONJ with bevacizumab was 0.3% in the blinded phase of the two randomized trials and 0.4% in the single-arm study. There was trend toward increased ONJ incidence in patients who received BP therapy versus those with no BP exposure (0.9% vs. 0.2%, respectively, in the response to neo-adjuvant chemotherapy in locally advanced breast cancer? Clin Cancer J 2014;3:521-5.


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