CORRESPONDENCE

Re: HER2 Status and Efficacy of Adjuvant Anthracyclines in Early Breast Cancer: A Pooled Analysis of Randomized Trials

Gennari et al. (1) report an interaction between HER2 status and anthracycline chemosensitivity, but they do not mention tumor grade. Multivariable analysis has revealed that Scarff–Bloom–Richardson grade III tumors respond better to neoadjuvant treatment than Scarff–Bloom–Richardson grade I tumors ($P < .0001$) (2). A recent study suggests that an interaction between HER2 and estrogen receptor pathways may lead to higher proliferation rate and thus a higher tumor grade (3). Therefore, inclusion of tumor grade might have increased the relative predictive value of HER2 status and grade in predicting anthracycline chemosensitivity (2). Moreover, among patients who have HER2-negative, estrogen receptor–positive breast cancer, those with higher tumor grades may benefit from anthracycline (2). Furthermore, among patients who have HER2-negative, estrogen receptor–negative, and progesterone receptor–negative breast cancer, we have demonstrated a high rate of pathological complete response (4), which is an accepted surrogate of improved survival (5,6). Of the 15 patients who received four cycles of dose-dense anthracycline (doxorubicin) and cyclophosphamide followed by three cycles of paclitaxel (cremophor or albumin-bound paclitaxel) plus or minus carboplatin (both at 3 weeks on, 1 week off for one cycle) plus or minus six doses of bevacizumab every 2 weeks, 9 (60%; 95% confidence interval = 32% to 84%) achieved pathological complete response (4). Specifically, with anthracyclines given biweekly compared with every 3 weeks, there is a higher pathological complete response and, as a result, improved survival (7). Therefore, the pooled analysis needs to be replicated or refuted in the biweekly anthracycline setting, specifically in estrogen receptor–negative breast cancer.

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References

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Response
Dr Mehta correctly points out that there may be subgroups of HER2-negative patients who would benefit from the use of anthracycline-containing adjuvant chemotherapy, and she suggests that some anthracycline-containing regimens (especially the dose-dense ones) may be more effective than others. With regard to the first issue, individual patient data were not available for all studies in our meta-analysis, which was conducted on published data; as a consequence, the subgroup analyses she advocates are not possible. However, two points must be stressed. First, this hypothetical subgroup of anthracycline-sensitive patients, if it does indeed exist, is likely to be quite small; otherwise, to explain the lack of any effect in the overall group of HER2-negative patients observed in our analysis (hazard ratio for disease-free survival = 1.00; 95% confidence interval [CI] = 0.90 to 1.11; $P = .75$, hazard ratio for overall survival = 1.03; 95% CI = 0.92 to 1.16; $P = .60$), it would be necessary to assume that anthracyclines are detrimental in the remaining hypothetically unsensitive patients, a rather implausible hypothesis. Second, the high sensitivity to chemotherapy of high-grade breast tumors mentioned by Dr Mehta, per se, does not indicate that these tumors are more sensitive to anthracycline-containing regimens than to other regimens: to our knowledge, there are no reports linking higher grade to increased sensitivity to anthracyclines. As far as dose intensity is concerned, three studies (1–3) have indicated that dose-dense anthracycline-based regimes are more effective than standard density regimes in HER2-positive patients but not in HER2-negative patients, indirectly supporting our conclusions and confirming that the differential sensitivity to anthracyclines, according to HER2 status, may have a molecular basis. Finally, we agree with Dr Mehta that choosing the appropriate adjuvant therapy for triple negative (ie, HER2-, estrogen receptor–, and progesterone receptor–negative) patients is challenging and that new studies or meta-analyses of previous studies that are based on individual patient and tumor data are needed to answer this question.

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