Re: Neoadjuvant Versus Adjuvant Systemic Treatment in Breast Cancer: A Meta-Analysis

The meta-analysis by Mauri et al. (1) from nine neoadjuvant trials is important given the conflicting evidence from published studies. However, we would like to make two points that arise from this analysis.

First, to establish the benefit of neoadjuvant therapy over adjuvant therapy, treatment regimens in the two arms should be identical in terms of drugs used and in terms of scheduling. Mauri et al. acknowledged that postoperative chemotherapy was administered to patients randomly assigned to the neoadjuvant arm in approximately half of studies (2–5), representing approximately a quarter of the dataset pooled (986 patients). This sizeable proportion may have biased results in favor of adjuvant therapy. Ideally, these studies should have been excluded from pooling, but this exclusion would have resulted in pooled data available on only 2960 patients, of which a few more than half (1523 patients) would have been from a single study [National Surgical Adjuvant Breast and Bowel Project B-18 (6)]. Data from sensitivity analysis with and without the four studies (2–5) in which patients received both adjuvant and neoadjuvant chemotherapy should be obtained to assess their potential impact on the primary outcomes assessed and the robustness of the authors’ conclusions.

Second, Mauri et al. focused on the inability of neoadjuvant chemotherapy to improve any of the primary outcomes assessed, compared with adjuvant therapy, but this analysis should be recognized as a success. Data presented show the clear superiority of neoadjuvant therapy in breast-conserving surgery, an important issue for many patients. Furthermore, the ability to obtain tumor tissue by core biopsy before and during neoadjuvant therapy, in addition to the surgical specimen itself, offers a major opportunity for translational research.

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RESPONSE

Popat and Smith question whether the results of the meta-analysis are robust to the exclusion of studies in which not all cycles of chemotherapy in the neoadjuvant arm were administered preoperatively. As shown also in Fig. 1 of our meta-analysis (1), sensitivity analyses that excluded these four studies yield practically identical results to what we saw when all studies were included. Specifically, if we exclude these studies, there is still a statistically significant increase in the risk of loco-regional recurrences with neoadjuvant treatment (fixed effects risk ratio [RR] = 1.30, 95% confidence interval [CI] = 1.08 to 1.55, P = .005; random effects RR = 1.32, 95% CI = 1.06 to 1.64, P = .014). Neoadjuvant regimens have outcomes equivalent to those of adjuvant regimens for death (fixed effects RR = 1.01, 95% CI = 0.90 to 1.13), disease
progression (fixed effects RR = 1.01, 95% CI = 0.92 to 1.10), and distant disease progression (fixed effects RR = 0.90, 95% CI = 0.78 to 1.05).

As discussed also in the meta-analysis, the rates of conservative local treatment with neoadjuvant versus adjuvant therapy varied considerably across trials (1), but this result was not the focus of the meta-analysis. The choice of a conservative local treatment may depend on a variety of factors, including tumor diameter, regimen used, response, and subjective preferences of the patient and treating physician. However, the meta-analysis cautions that the use of too conservative means for local treatment (in particular use of radiotherapy without any surgery at all) entails a statistically significant risk of subsequent local recurrence.

Finally, the opportunity to perform translational research on core biopsy specimens is welcome, but of course this research is limited to research settings and cannot be generalized to all patients outside of clinical trials. Promising translational approaches may be worthwhile to pursue further, but their wide adoption requires solid clinical documentation (2, 3).

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