In their review of combination vs sequential single-agent chemotherapy in advanced breast cancer, Cardoso et al. (1) highlight nine recent randomized trials and suggest that previous meta-analyses were heavily biased by the inclusion of clinical trials testing outdated chemotherapy regimens with serious methodological flaws, which often failed to mandate crossover. Although in general we are in agreement with their assessment, we submit that two other randomized clinical trials evaluating combination vs sequential chemotherapy met their posed criteria. The use of cyclophosphamide, methotrexate, 5-flourouracil–based chemotherapy remains an active option in breast cancer management. In two studies (2,3), the Western Cancer Study Group and the Southeastern Cancer Study Group conducted trials of similar design comparing concomitant combination treatment or sequential use of the same drugs given as single agents changed only at disease progression. In both trials, cyclophosphamide, methotrexate, 5-flourouracil, and prednisone were used; the Western Cancer Study Group used triiodothyronine and the Southeastern Cancer Study Group used vincristine as the remaining agent. The trials were originally reported separately, but a common updated database was created and a combined analysis performed (4). Of 220 randomized patients, 210 had died and 70% of women in the monotherapy arms received the protocol mandated crossover therapy. Combination treatment was associated with statistically significantly increased objective response frequency (46% vs 25%, P < .05) but no survival benefit. For patients without liver metastases, survival was closely comparable in the treatment groups. However, combination therapy increased overall survival for those with liver involvement (median 10.1 vs 5.3 months, respectively) (P < .05) (4). This combined analyses of the two trials included more patients than five of the nine trials cited by Cardoso et al. and had a higher crossover frequency than seven of the nine cited trials. The conclusions reached from the study published in 1989, which mainly evaluated agents that are still used as standard therapy for breast cancer, support those emanating from the more recent evaluation of this topic.

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References

Notes
Cardoso et al. declined the invitation to respond. R. T. Chlebowski is on the speaker’s bureau for Sanofi Aventis, the maker of a drug used for breast cancer chemotherapy.

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