

CORRESPONDENCE

Phase II Studies: Untreated Breast Cancer Patients

Since current drugs, given either singly or in combinations, do not cure metastatic breast cancer, it is always exciting to see new, promising agents for the treatment of this disease. Two recently reported phase II studies (1,2) described two new and highly active agents for the treatment of breast cancer: anthracycline CI941 (1) and taxol (2). Almost half of the patients studied had had no prior chemotherapy for their metastatic disease. A discussion about the wisdom and safety of omitting optimal therapy as a first treatment was ignored in these reports. What is the risk (or benefit) of using unproven agents in phase II trials before administering standard chemotherapy?

There is a pressing need to discover new active agents for the treatment of advanced breast cancer, since current regimens, although active, are essentially palliative; i.e., they do not cure patients with metastatic disease (3-6). It is therefore highly unlikely that recombination or new schedules of existing drugs will result in any substantial treatment advances. Consequently, the testing of new drugs is of the utmost importance if we are to make progress in the treatment of metastatic breast cancer. The almost universal practice of testing these agents in patients who have been heavily pretreated is a significant limitation in our current phase II drug studies. The performance of active phase II agents in this setting is certain to be inferior to that which would have been observed in previously untreated patients. Indeed experience with doxorubicin as a phase II agent demonstrated a strikingly poor response (7). The attempt to discover active drugs through the usual phase II mechanism is imperfect and perhaps self-defeating by its very design (8,9). If further advances in

the treatment of breast cancer are to be made, the current clinical model for phase II testing must be changed. A more useful model would permit the testing of phase II agents as first-line therapy followed by standard chemotherapy. The adoption of this new model would open the way for a realistic evaluation of phase II drugs and, in effect, provide a drug discovery strategy.

However, for such a model to be widely accepted, it must be demonstrated that the overall outcome (i.e., survival and cumulative response rate) for patients treated with potentially ineffective single-agent therapy followed by conventional chemotherapy is better or at least as good as that for patients treated initially with conventional chemotherapy. To test the model, the Cancer and Leukemia Group B has a large, ongoing randomized trial (CALGB 8642) designed to evaluate the risk (or benefit) of using phase II agents "up front" in previously untreated breast cancer patients. Meanwhile, testing unknown and potentially ineffective or less effective agents up front should be curtailed until the results of the CALGB 8642 trial are mature. What can we say about using a highly active single phase II agent such as taxol or anthracycline CI941 before standard therapy? Agents such as these, which attain a 30%-50% response rate, are comparable to standard therapy and are probably not harmful. We should remember, however, that these two agents were not, in the true sense, unknown phase II agents, since their activity was already evident in pretreated patients.

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Relationship Among Prognostic Laboratory Indices in Breast Cancers

We read with great interest the recent brief communication by Ciocca et al. (1) on the correlation of HER-2/neu oncogene amplification with other breast cancer prognostic indices. We have been involved in a similar study and have, in press, a paper (2) describing the relationship between the amplification of HER-2/neu (or c-erbB-2, the designation we have chosen) and estrogen and progesterone receptors in a somewhat larger group of 1532 tumors.

In most respects, our data are similar to those in the brief communication by Ciocca et al. (1). We found highly significant correlations between receptor negativity and c-erbB-2 amplifications (positive c-erbB-2 amplification versus estrogen receptor negativity = $P < 10^{-4}$; positive c-erbB-2 amplification versus progesterone receptor negativity = $P < 10^{-4}$) by using a contingency table model and evaluating the resulting χ^2 values. Among the 217 tumors in which oncogene amplification was present, 102 (47.0%) were estrogen receptor positive. In the 1315 tumors