Re: erbB-2, p53, and Efficacy of Adjuvant Therapy in Lymph Node-Positive Breast Cancer

One of the current emphases in biologic research in breast cancer is a shift toward factors that predict benefit from therapy, as opposed to those that relate to the prognosis for a patient. This is to be welcomed, but in the move, the ground rules already established for assessing the validity or otherwise of putative factors should not be ignored. It was therefore disappointing that the latest report on the CALGB 8541/8869 studies that assess the potential interaction between c-erbB-2 expression and dose intensity of adjuvant doxorubicin did not fully comply with the guidelines published by the late W. L. McGuire 7 years ago in this same journal (1). The confirmatory study by Thor et al. (2) clearly failed to confirm the earlier pilot study by Muss et al. (3), which had reported that benefit from the higher dose intensity of doxorubicin-based adjuvant therapy was only to be seen in patients whose tumors have high expression of c-erbB-2. Apart from a possible population bias in that the larger, confirmatory group was inevitably itself drawn from the patients in the original 8541 study, this negative conclusion concurred with Dr. McGuire’s proposed guidelines.

The problem, however, lies in the attempt to explain this negative confirmatory report by developing a prognostic model for the disease-free survival of the patients studied. In so doing, the authors failed to comply with four of Dr. McGuire’s seven guidelines. First, there was no clear biologic hypothesis for the negative term for estrogen receptor (ER) quite apart from the problems that the presence or absence of ERs was not significant for disease-free survival in the univariate or multivariate analyses presented in the paper; and the fact that expression of ER has been reported to violate an essential assumption for inclusion in a Cox proportional hazards model, namely, that the hazard ratio should be independent of time (4)]. Second, there was no random allocation of the patients into an exploratory and confirmatory group for validation of this new prognostic model. Third, no sample-size calculation is presented to confirm that the population studied was of sufficient size to empower the prognostic model. Fourth, there is an inherent possible population bias in that the population on which the prognostic model was derived constituted the patients under scrutiny and represented less than two thirds of the entire cohort in CALGB 8541. Furthermore, the three of the remaining McGuire guidelines are not really applicable to the proposed index.

It is clearly of importance to the Oncologic community, physician and patient alike, to know if there is a genuine interaction between the dose intensity of adjuvant anthracycline and outcome of women whose tumors have high expression of c-erbB-2, but this study, as presented, can only be interpreted as a negative confirmatory study. The application of an independently produced and validated prognostic model, such as that developed by the Nottingham group (5), is required before there is any conclusion other than that this study fails to confirm the earlier findings reported by Muss et al. (3).

DAVID A. CAMERON
ROBERT C. F. LEONARD

REFERENCES


NOTES

Affiliation of authors: Department of Oncology, Western General Hospital, Edinburgh, U.K.
Correspondence to: D. A. Cameron, M.D., F.R.C.P., Department of Oncology, Western General Hospital, Crewe Rd., S., Edinburgh, EH4 2XU, U.K.

RESPONSE

We agree with some of the points made by Drs. Cameron and Leonard. However, we disagree that our study (1) “clearly failed to confirm” our earlier study (2). We presented the current study’s results and gave arguments from both points of view: that it confirms and that it does not confirm. Cameron and Leonard take the latter perspective. We address their points in this response, but we also address the more important issue of whether the available evidence is sufficient to conclude that patients with node-positive breast cancer who overexpress erbB-2 should receive higher doses of doxorubicin and that patients who express erbB-2 at normal levels can reasonably avoid this drug.

In our article (1), we considered 595 patients and compared their outcomes with those of 397 patients we had reported earlier. We showed that the survival curves for patients receiving high-dose CAF (cyclophosphamide, doxorubicin, and 5-fluorouracil) were quite similar in the two sets—for both erbB-2 overexpressors and normal expressors. We also showed that the same was true for the corresponding standard-dose groups. Moreover, in both sets, erbB-2 overexpressors responded substantially better on high-dose CAF than on standard-dose CAF but normal expressors did not. In addition, survival for normal expressors on low-dose CAF was very similar in the confirmatory and original sets, with no dose effect among normal expressors. So far, so good. The subgroups that disagree in the two sets are the erbB-2 overexpressers receiving low-dose
CAF. In the original set, these patients had disease recurrence or died early, but in the confirmatory set, they showed very good survival. Although the latter group’s performance was not as good as the performance among erbB-2 overexpressors receiving high-dose CAF in the confirmatory set, it was better than that of erbB-2 overexpressors who received standard dose.

This might lead to a conclusion that our study was not confirmatory, as we indicated in our article. However, we pointed out an alternative explanation. As chance would have it, erbB-2 overexpressors on low-dose CAF in the confirmatory set (n = 52) had the best prognosis of any subgroup of patients (where “prognosis” does not count erbB-2 status or dose of CAF). In particular, they on average had 40% fewer positive axillary lymph nodes (P < 0.05) and 50% greater tamoxifen use (P < 0.05) than the erbB-2 overexpressors on low-dose CAF in the original set. This led us to adjust prognoses of all patients, with the result that the interaction between CAF dose and erbB-2 expression became comparable in the two sets, although the interaction was still stronger in the original set than in the confirmatory set. For this reason and also because our adjustment was post hoc, some readers may find this adjustment less than compelling.

Cameron and Leonard focused on our prognostic index and criticized it on several grounds. They suggest that we should have used an index developed independently, such as one from the Nottingham group (3). In fact, the index used matters very little and virtually any index that considers the number of positive lymph nodes and the use of tamoxifen would give the same result. (The Nottingham index considers neither of these: it includes lymph node stage—all patients in our study had positive lymph nodes—but not number of positive lymph nodes, and it does not consider tamoxifen use.) Considering the number of lymph nodes alone would go a long way toward the conclusion we drew based on our index, and the same is true for tamoxifen use. With regard to the negative contribution of being estrogen receptor positive (ERPOS) in the index, this is explained in our article as the result of the correlation between ERPOS and the use of tamoxifen. However, the coefficient for ERPOS is small and dropping ERPOS from the index entirely would change none of our conclusions. The three other issues that concern Cameron and Leonard are the lack of confirmation of the index, the possibility of an inadequate sample size of the set on which the index is based, and the possibility of bias in the patients used. Our conclusions are not at all sensitive to the index used, and we were remiss in not pointing this out. We calculated similar indices based on 1) patients in CALGB (Cancer and Leukemia Group B) 8541 who were not in our study, 2) patients in the confirmatory study only, 3) patients in the original study only, and 4) patients in the full CALGB 8541 study (4). There is no essential difference in the index and no difference in the overall conclusion based on adjusting the survival curves.

We suggested above that a question more important than whether our study was confirmatory is whether the conclusion is real and whether it should be used in the management of patients with breast cancer. Our original observation (2) was based on an exploratory analysis that was not prescribed in the study protocol. As a result, and because of its substantial clinical implications, we examined a number of databases to confirm or deny it (5). When we focused on patients who had received doxorubicin, we found that those with tumors overexpressing erbB-2 remained disease free as long or longer than those with tumors expressing at normal levels. On the other hand, when we focused on patients not receiving doxorubicin, we found that those with tumors overexpressing erbB-2 recurred much sooner than did normal expressors. Our rationale and the details of the trials and databases and their analyses are given by Berry et al. (5). These analyses gave us confidence that our observation was not a fluke, and, therefore, we published it (2). That this was appropriate has been verified by studies from the National Surgical Adjuvant Breast and Bowel Project (6) and from the Southwest Oncology Group (7). The corpus of available information convinces us that there is a genuine interaction between erbB-2 and doxorubicin in node-positive breast cancer and that this interaction is clinically relevant.

DONALD A. BERRY
ANN D. THOR

REFERENCES


NOTES

Affiliation of authors: Institute of Statistics and Decision Sciences, Duke University Medical Center, Durham, NC.

Correspondence to: Donald A. Berry, Ph.D., Institute of Statistics and Decision Sciences, Duke University Medical Center, 223 Old Chemistry Bldg., ISDS, Box 90251, Durham, NC 27708-0251 (e-mail: db@stat.duke.edu).