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ORIGINAL ARTICLE

Tailoring adjuvant treatments for the individual breast cancer patient

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SUMMARY. Background: Chemotherapy, tamoxifen and ovarian function suppression have all demonstrated their effectiveness for treating women with early breast cancer. Treatment selection for individual patients, however, requires estimates on the magnitude of treatment effects to be achieved from the application of each modality. Unfortunately, information currently available is insufficient to properly tailor adjuvant treatments.

Methods: We consider predictive factors to improve our understanding about selection of adjuvant therapies, reassessment of data from previous clinical trials and design of future studies.

Results: Estrogen receptor (ER) and progesterone receptor (PgR) are the primary measures available today to tailor adjuvant therapies. Patient age/menopausal status (ability to obtain treatment effects via ovarian function suppression), measures of the metastatic potential of the tumor (such as number of positive axillary lymph nodes), and concurrent use of chemotherapy and tamoxifen are other factors that modify the magnitude of relative effect associated with chemotherapy and endocrine therapies. The Subpopulation Treatment Effect Pattern Plots (STEPP) method displays the patterns of treatment effects within randomized clinical trials or datasets from meta-analyses to identify features that predict responsiveness to the treatments under study without relying on retrospective subset analysis. Confirmation of hypotheses using independent clinical trial databases is recommended.

Discussion: All findings from clinical trials and meta-analyses should be presented primarily according to steroid hormone receptor status and patient age. Future studies should be designed as tailored treatment investigations, with endocrine therapies evaluated within populations of patients with endocrine responsive tumors, and chemotherapy questions focused within populations of patients with endocrine nonresponsive disease.

Keywords: Breast cancer; Adjuvant therapy; Predictive factors; Chemotherapy; Tamoxifen; Estrogen receptor; Progesterone receptor; STEPP

INTRODUCTION

Many of the presentations at the 8th International Conference on the Primary Therapy of Early Breast Cancer[1] described the potential of gene expression profiling and proteomics for individualizing treatment decision-making. While holding promise for the future, the new technologies require further study and validation before becoming clinically useful. Meanwhile, several factors are available that can predict the magnitude of response to adjuvant systemic therapy, but they are not always used for treatment selection. Furthermore, the discouragement of examining treatment effects within patient subgroups reduces the

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opportunity to properly explore the relative effect of different therapeutic modalities and hinders tailored treatment.

Prognostic factors serve to characterize the background level of risk of relapse against which the benefits and burdens of adjuvant therapies are weighed. *Predictive factors* are inextricably linked to the specific treatment for which responsiveness is defined and, thus, are key for defining tailored treatment approaches for subpopulations of patients. Better use of predictive factors is essential both to define future clinical investigations as well as to extract the patient-oriented information obtained from existing databases.

METHODS

In this paper, we assert that current methods used to present results from clinical trials are inadequate to properly tailor treatments. The Subpopulation Treatment Effect Pattern Plots (STEPP) method explores the patterns of treatment effects obtained from subpopulations within randomized clinical trials or datasets from meta-analyses to help identify features that predict responsiveness to the treatments under study.[2–4] Generation of biologically plausible hypotheses to be tested further using datasets from other clinical trials is recommended.[5]

RESULTS

Role of estrogen receptor to predict treatment response

Estrogen receptor (ER) and progesterone receptor (PgR) are the most important factors used today to tailor adjuvant therapies. Unfortunately, steroid hormone receptor status has not been routinely used when results of clinical trials assessing chemotherapy effects are presented. Separate analyses for patients with endocrine responsive and endocrine nonresponsive disease are essential to better understand the effectiveness of chemotherapy in conjunction with effective endocrine treatments.

Several factors must be considered to properly assess the magnitude of chemotherapy effects in future studies. (1) Measurement of ER and PgR in the primary tumor is required. (2) Assays should be done using quality-controlled procedures, preferably in a high volume laboratory (at least 250 assays performed per year). (3) Quantitative results (rather than merely positive or negative) should be reported to provide a better tailoring. (4) Tumors with no expression of receptors (ER- and PgR-absent) should be distinguished both from those with low levels of expression (ER- or PgR-low) and from those with positive level of expression (ER- or PgR-positive). These features should be considered both for care of patients today and for interpretation of results from clinical trials that were conducted and reported in the past. A growing body of evidence, including observations from clinical trials[6–8] as well as gene profiling studies,[9] indicates that ER- and PgR-absent tumors are distinct from other forms of breast cancer.

The following examples illustrate that quantitative assessment of ER, nodal status and sequential vs concurrent use of CMF chemotherapy and tamoxifen should influence selection of adjuvant treatment for postmenopausal women.

International Breast Cancer Study Group (IBCSG) Trial VII

IBCSG Trial VII enrolled 1212 postmenopausal patients with node-positive disease between 1986 and 1993 to evaluate tamoxifen alone for 5 years, vs tamoxifen plus three courses of 'classical' CMF in months 1, 2, 3, vs tamoxifen plus three delayed courses of CMF in months 9, 12, 15, vs tamoxifen plus both early and delayed CMF.[10] Tamoxifen was given concurrently with the chemotherapy and was administered for the duration of 5 years in all treatment groups. The randomization was prospectively stratified by ER-status of the primary tumor.

We previously reported a detrimental effect of late initiation of CMF at 9, 12, 15 months concurrent with tamoxifen that had been initiated 9 months earlier.[3,10] This detrimental effect was seen exclusively among patients with ER-negative tumors. Those with ER-positive disease benefited from the addition of chemotherapy together with tamoxifen irrespective of the timing and duration of the chemotherapy.

In this report, we focus on the IBCSG Trial VII comparison between patients in the tamoxifen alone group ($n = 306$) and those in the group randomized to receive three initial course of CMF concurrently with the initiation of tamoxifen ($n = 302$). Figure 1 shows the Kaplan–Meier curves for disease-free survival for these two arms at 11 years of median follow-up. The result for all patients (Fig. 1A) shows an advantage associated with adding the chemotherapy that is not statistically significant. The magnitude of the effect appears to be similar irrespective of the ER-status of the primary tumor (Figs 1B and C), although patients with ER-negative disease appear to gain slightly less from the chemotherapy (Fig. 1B) compared with those having

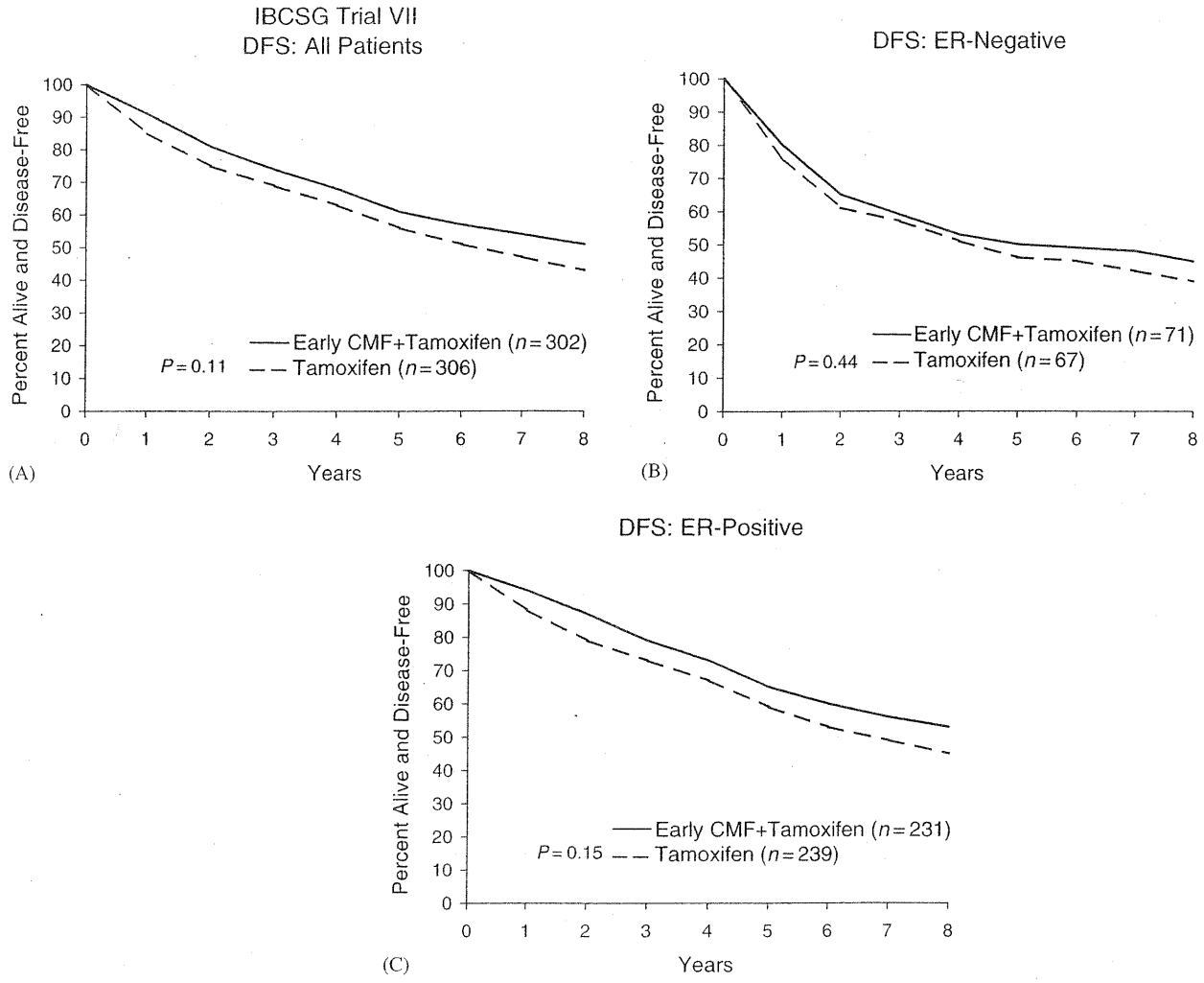

Fig. 1 Kaplan–Meier plots of disease-free survival (DFS) for early CMF × 3 plus tamoxifen × 5 years and for tamoxifen alone × 5 years in IBCSG Trial VII for postmenopausal women with axillary lymph node-positive breast cancer. The median follow-up was 11 years. Results are shown for all 608 patients (panel A), for 138 patients with ER-negative tumors (panel B), and for 470 patients with ER-positive disease (panel C). The 5-year DFS percents for early CMF plus tamoxifen vs tamoxifen alone were 61% vs 56% (panel A), 50% vs 46% (panel B) and 65% vs 59% (panel C).

ER-positive disease (Fig. 1C). Notice in addition that the shapes of the curves differ according to ER-status. Relapses occur earlier among the ER-negative cohort and then the curves appear to level off. The DFS curves for the ER-positive cohort are not as steep in the early follow-up period, but continue to decline as follow-up continues. This pattern has been observed in many series and provides additional evidence that ER-negative and ER-positive tumors represent at least two different diseases, thus requiring a tailoring of treatment.

International Breast Cancer Study Group (IBCSG) Trial IX

While IBCSG Trial VII investigated the role of concurrent CMF and tamoxifen for patients with node-positive disease, IBCSG Trial IX investigated the role of CMF administered prior to tamoxifen for patients with node-negative disease. For Trial IX, 1669 eligible patients with node-negative breast cancer were randomized to receive either tamoxifen for 5 years or three courses of 'classical' CMF followed by tamoxifen to complete 5 years of treatment.[11] The randomization was prospectively stratified according to ER status.

At a median follow-up of 7 years, adding CMF prior to tamoxifen significantly improved DFS ($P=0.04$) (Fig. 2A). In contrast to IBCSG Trial VII, however, the effectiveness of adding CMF to the adjuvant treatment regimen was observed exclusively among patients with ER-negative disease (Fig. 2B). No difference in treatment outcome was observed for patients with ER-positive tumors (Fig. 2C). A recent

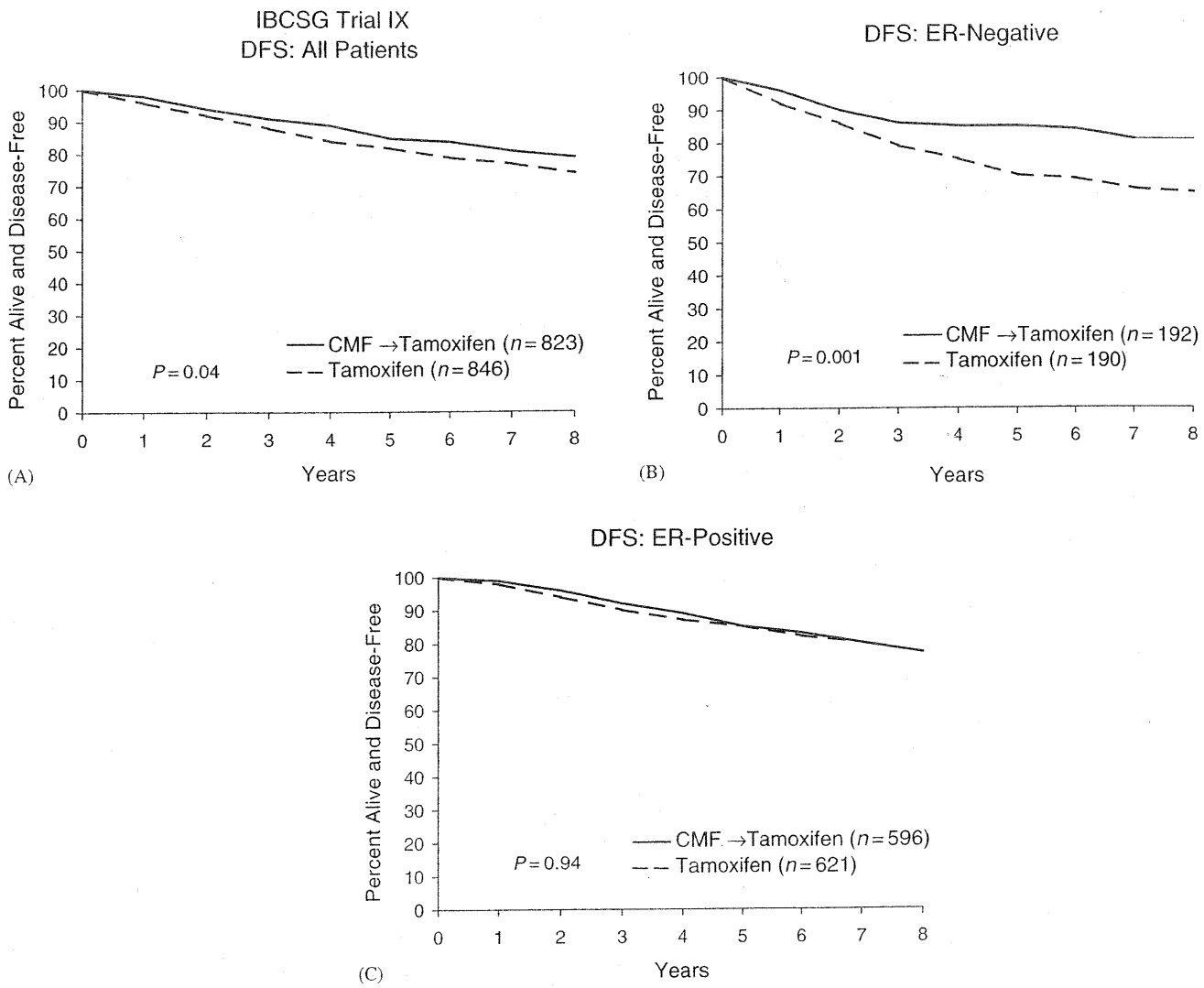

Fig. 2 Kaplan–Meier plots of disease-free survival (DFS) for CMF × 3 followed by tamoxifen × 57 months and for tamoxifen alone × 5 years in IBCSG Trial IX for postmenopausal women with axillary lymph node-negative breast cancer. The median follow-up was 7 years. Results are shown for all 1669 patients (panel A), for 382 patients with ER-negative tumors (panel B), and for 1217 patients with ER-positive disease (panel C). The 5-year DFS percents for CMF followed by tamoxifen vs tamoxifen alone were 85% vs 82% (panel A), 85% vs 70% (panel B) and 85% vs 85% (panel C).

reanalysis of the NSABP B-20 study confirmed the absence of benefit for adding chemotherapy to tamoxifen for postmenopausal women with lymph node-negative, ER-positive breast cancer.[12]

Many statisticians discourage subset analyses such as those presented above according to ER status for Trials VII and IX. The prohibition is somewhat less stringent in these cases as the randomizations were prospectively stratified by ER status. Nevertheless, extreme caution is usually recommended and readers are urged to avoid applying results from subset analyses to guide treatment decision-making. There are sound statistical arguments supporting such cautious interpretation of findings based upon retrospective subset analyses when they are significant exclusively in the current analysis and not motivated by previous biologically plausible hypotheses. However, to facilitate proper treatment choice for individual patients, much more attention should be given to subset analyses that have been independently confirmed.[5]

Subpopulation Treatment Effect Pattern Plots (STEPP)

One difficulty with subset analyses is the arbitrary grouping of patients into subgroups. For example, the results presented above are for ER-negative and ER-positive cohorts. Yet, quantitative assessment of ER was

available for a large number of women in the above trials (ligand-binding assays were performed during the 1990s). Rather than using a dichotomizing subset analyses, we developed an alternative methodology called Subpopulation Treatment Effect Pattern Plot (STEPP). STEPP was developed to examine the pattern of treatment differences across a sequence of overlapping patient subpopulations defined by a covariate of interest (e.g., quantitative ER).[2–4] STEPP is particularly informative for evaluating treatment effects with respect to a continuous covariate. Treatment effects can be expressed as relative risk estimates obtained from Cox models,[2] differences in means or proportions, or estimates of 5-year DFS.[3,4] A test of statistical significance for the interaction between treatment effect and the potential predictive factor is based on the maximum difference between any of the subgroup treatment effects and the overall treatment effect.[3,4]

Figure 3 shows the STEPP analysis of 5-year DFS for IBCSG Trial VII (Fig. 3A) and for IBCSG Trial IX (Fig. 3B) according to quantitative values of ER. Approximately 120 patients were included in each subpopulation for the Trial VII analysis, and approximately 200 per subpopulation for the Trial IX analysis. Subsequent overlapping subpopulations were defined moving from left to right by dropping approximately 10 patients with the lowest values of ER and adding approximately 10 patients with the next higher values of ER. For each subpopulation, the 5-year DFS percents for endocrine therapy and chemoendocrine therapy groups were estimated with the Kaplan–Meier method.

The patterns of treatment differences illustrated in the STEPP analyses according to ER value were very different for the Trial VII (node-positive, concurrent CMF plus tamoxifen) and for the Trial IX (node-negative, sequential CMF followed by tamoxifen). For Trial VII, we see little treatment difference for the lowest values of ER, a growing separation favoring the CMF-containing regimen for intermediate values (in the ER-positive cohort), and then a coming together for higher values of ER expression. This pattern of treatment differences explains why the previously reported subset analyses showed little effect for ER-negative and a positive effect for ER-positive cohorts. The detrimental effect of concurrent tamoxifen and CMF for the ER-negative cohort, and the heterogeneous nature of tumors for a node-positive population may explain this pattern of treatment effect according to quantitative ER.

In contrast, for Trial IX, the STEPP analysis indicates that the CMF is effective exclusively for the lowest values of ER and no difference is observed as ER expression increases above the lowest values. For Trial IX, the pattern reveals a clear separation between cytotoxic and endocrine therapy effectiveness.[13] The sequential rather than concurrent use of tamoxifen and CMF, and the more homogeneous nature of tumors for a node-negative population may explain this pattern of treatment effect according to quantitative ER.

DISCUSSION

There is an increasing consensus that proper assessment of ER and PgR is required to guide treatment for breast cancer patients in the adjuvant setting.[1] Results of clinical trials that are used to select adjuvant therapy should be re-examined separately according to steroid hormone receptor-negative and -positive cohorts. Ideally a separation into absent, low and positive levels of expression should be attempted. Subset analysis according to receptor status is routinely made for clinical trials

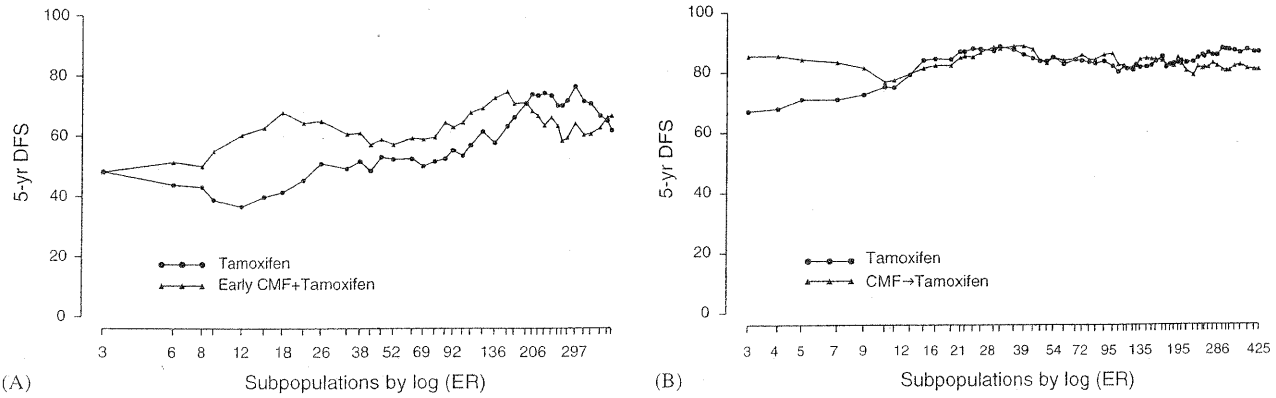

Fig. 3 STEPP plots of 5-year DFS percents for IBCSG Trial VII comparing early CMF plus tamoxifen vs tamoxifen alone (panel A) and for IBCSG Trial IX comparing CMF followed by tamoxifen vs tamoxifen alone (panel B) according to quantitative ER values (fmol/mg cytosol protein) of the primary tumor. Numbers on the *x*-axis refer to the median value of ER (ligand-binding assay) for each of the overlapping subpopulations used to perform the STEPP analysis.

that assess the effectiveness of endocrine therapies. Unfortunately, the same separation is rarely performed as part of the primary analysis for trials that investigate the effectiveness of chemotherapy. Such analyses are required to obtain proper estimates of the magnitude of treatment effects needed to individualize therapeutic decision making. Figure 4 in the 1998 publication of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) polychemotherapy overview showed a much larger chemotherapy effect for node-negative as compared with node-positive disease among women who were 50 years of age or older.[14] The apparent anomaly was attributed to the play of chance and estimates of the magnitude of chemotherapy effect were summarized according to age and risk of relapse.[14] Evidence exists, however, that differences in outcome reported according to nodal status were really due to differences in steroid hormone receptor status and concurrent use of tamoxifen for older women who were enrolled in the trials of chemotherapy vs no chemotherapy for the node-negative and node-positive populations.[5,15,16] It is hoped that the next publication of the EBCTCG polychemotherapy overview will present results primarily according to ER-status, age and nodal status rather than just age and nodal status alone.

The STEPP method was developed to assess the patterns of treatment differences according to a covariate of interest, as opposed to the usual dichotomized subset analyses. The method has been used to highlight the role of patient age in randomized comparisons of three courses vs six courses of CMF.[17] The differences favoring six courses were restricted to the youngest patients (less than 40 years old) or those having ER-negative disease; three courses did just as well as six for patients 40 years and older with ER-positive disease. Patients did not receive tamoxifen in these trials.[17]

In the current paper, we applied the STEPP method to assess differences in treatment effect (tamoxifen vs CMF plus tamoxifen or CMF followed by tamoxifen) according to quantitative ER values for postmenopausal women. Differences in the pattern of treatment effects were observed between IBCSG Trial VII (node-positive, concurrent CMF and tamoxifen) and IBCSG Trial IX (node-negative, sequential CMF followed by tamoxifen). Some of the difference between the two STEPP analyses might be due to the concurrent rather than sequential use of CMF and tamoxifen. Concurrent use may be detrimental for patients with ER-negative disease,[3,10] and recent results indicate that sequential use is superior to concurrent for patients with ER-positive disease.[18] Laboratory evidence also supports an antagonistic interaction between some chemotherapy agents and antiestrogens.[19]

Another factor could be the ability of the ligand-binding assay assessment of ER-status to more precisely distinguish between endocrine responsive and endocrine nonresponsive disease for patients with node-negative disease compared with those in the node-positive cohort. Primary breast cancer tumor cells are likely to be more heterogeneous if there is evidence of spread to axillary lymph nodes than if metastatic potential has not yet been demonstrated. Thus, an intermediate amount of ER expression in the presence of axillary lymph node-positive disease may not be sufficient to rule out the presence of chemotherapy sensitive clones in the primary tumor. In contrast, for patients with axillary lymph node-negative disease, ER-positive status is sufficient to identify a population of patients for whom adding chemotherapy to a regimen of endocrine therapy is not worthwhile. It is clear that the mechanisms of treatment responsiveness and resistance are more complex and multi-faceted than described above.[20] However, data available today from clinical trials suggest that qualitative interactions are much more likely to be real than previously postulated and that a greater willingness to further investigate and report biologically supported subset analyses is required.

We are not proposing an indiscriminant reliance on retrospective subset analyses for individualizing treatment. However, use of independent datasets to validate unexpected results that are biologically plausible is strongly recommended. For example, a review of the IBCSG database of premenopausal patients who had received adjuvant chemotherapy but no endocrine treatment showed that those less than 35 years old with ER-positive disease had a much worse disease-free survival than other women included in the analyses.[21] Other cooperative groups were invited to collaborate on a project to determine whether the same result could be confirmed in this very rare cohort of women. The results examined by NSABP, SWOG and ECOG supported the original IBCSG finding.[22] It is now quite clear that chemotherapy alone is insufficient adjuvant treatment for very young women with ER-positive breast cancer.

To increase our knowledge about how to individualize adjuvant treatment for premenopausal women with ER- and/or PgR-positive disease, three complementary clinical trials (tailored treatment investigations) are being conducted by the Breast International Group (BIG) and the North American Breast Intergroup to assess the role of ovarian function suppression (OFS), to examine the relative merits of exemestane and tamoxifen, and to study the role of chemotherapy (when added to OFS and either exemestane or tamoxifen). The three trials are being coordinated by the IBCSG and are known as

SOFT, TEXT and PERCHE. The suppression of ovarian function trial (SOFT) is for patients who remain premenopausal following chemotherapy or for whom tamoxifen alone is considered a reasonable treatment. The tamoxifen and exemestane trial (TEXT) and the premenopausal endocrine responsive chemotherapy trial (PERCHE) are for patients with no prior adjuvant or neoadjuvant therapy.[23,24] Additional information about these tailored treatment investigations is available on the IBCSG website: www.ibcsg.org.

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Appendix I: International Breast Cancer Study Group (IBCSG). Participants and Authors Trials VII and IX; Updated: April 2003

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