The Breast (2005) 14, 582–593

THE BREAST

www.elsevier.com/locate/breast

ORIGINAL ARTICLE

Predicting response to systemic treatments: Learning from the past to plan for the future

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KEYWORDS
Breast cancer;
Predictive factors;
Estrogen receptors;
Progesterone receptors;
Adjuvant therapy;
Chemotherapy;
Tamoxifen;
STEPP

Summary Therapeutic effects of adjuvant therapies for breast cancer have been assessed "across the board" and implemented using the principle that if a treatment is effective "on average" then it is effective "for all patients." Exploration and improved understanding of the biological basis for predicting response to available adjuvant therapies is essential to enhance patient care. As illustration, we consider the effects of chemotherapy and tamoxifen in two International Breast Cancer Study Group (IBCSG) trials for postmenopausal women. The level of estrogen receptor (ER) expression in the primary tumor is a powerful predictor of response to adjuvant therapy. Absence of ER identifies a chemosensitive cohort for which concurrent tamoxifen significantly blunts the large chemotherapy effect. High levels of ER expression are associated with good results using tamoxifen alone; adding chemotherapy provides little additional benefit. By contrast, adding chemotherapy to tamoxifen provides additional benefit for patients with node-positive disease and tumors expressing intermediate levels of ER. Identification of chemosensitive targets, e.g., absence of PgR, in tumors with intermediate ER expression is required to further tailor, adding chemotherapy within this otherwise endocrine-responsive cohort. Age is not a therapeutic target. Thus, the biological bases for treatment responsiveness must be defined. All findings from clinical trials and meta-analyses should be presented primarily according to steroid hormone receptor status and future studies should be designed as tailored treatment investigations.
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Introduction

Historically, adjuvant therapies for operable breast cancer have been studied "across the board" with little or no effort made to tailor clinical trials to populations of patients that might have the best chance of benefiting from the therapies being studied. Clinical trials and meta-analyses have been treatment focused—for example, assessing the role of chemotherapy, tamoxifen, ovarian ablation, etc.—rather than patient population focused. Patient age has been used as an easily

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0960-9776/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.breast.2005.08.021

identifiable feature for subgroup analyses, which has led to substantial misunderstanding and inappropriate use of age as a criterion for treatment choice.

Estrogen receptor (ER) and progesterone receptor are the most important factors used today to tailor adjuvant therapies.[1] 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. Quantifying the level of ER and PgR expression, rather than simply relying on positive and negative designations that produce a mixture of the degree of endocrine responsiveness, may be important to better define treatment response. For example, a growing body of evidence, including observations from clinical trials[2–4] as well as gene profiling studies,[5] indicate that ER- and PgR-absent tumors (those expressing no ER or PgR) are distinct from other forms of breast cancer. Endocrine therapies provide no benefit for patients with ER- and PgR-absent tumors; chemotherapy alone is very effective for this cohort.[1]

We present information relating to the role of adjuvant chemotherapy for postmenopausal patients with early stage breast cancer to illustrate how information from the past can be used to plan for the future. Data from two International Breast Cancer Study Group (IBCSG) trials serve as illustration. Our analyses are restricted to patients who were clearly postmenopausal at the time of enrollment in the clinical trial, rather than using an age cut-off of 50 years or older. In this way we eliminate the endocrine effects of chemotherapy associated with ovarian function suppression among older premenopausal women, and thereby provide an unconfounded assessment relevant for the postmenopausal cohort.

Key factors we consider are the level of ER expression in the primary tumor, the level of progesterone receptor (PgR) expression in the primary tumor, whether or not tamoxifen is given either sequentially or concurrently with chemotherapy, and finally nodal status. ER and PgR expression are predictive factors that are inextricably linked to the specific treatment for which responsiveness is defined. For example, endocrine therapies provide benefit in the presence of ER or PgR expression, but the magnitude of the benefit associated with tamoxifen may differ from that of an aromatase inhibitor depending on the level of ER and/or PgR expression.

We assert that current approaches for presenting results of clinical trials and meta-analyses are inadequate for properly tailoring treatments. The Subpopulation Treatment Effect Pattern Plots (STEPP) method explores the patterns of treatment effects across subpopulations defined by a covariate, e.g., ER level, to help identify features that predict responsiveness to the treatments under study in a randomized clinical trial or meta-analysis.[6–8] Generation of biologically plausible hypotheses to be tested further using datasets from other clinical trials is recommended.[9] We apply the STEPP method to the two IBCSG trials conducted for postmenopausal women to explore the role of ER and PgR in predicting response to chemotherapy.

Patients and methods

IBCSG Trial IX investigated the role of adjuvant chemotherapy administered prior to tamoxifen for patients with lymph node-negative disease. From 1988 to 1999, 1669 eligible postmenopausal patients with node-negative breast cancer were randomized to receive either tamoxifen for five years or three 28-day courses of ''classical'' CMF followed by tamoxifen to complete five years of treatment.[10] The randomization was prospectively stratified according to ER status of the primary tumor. Approximately 70% of the trial patients had ER and PgR measured by an extractive assay (fmol/mg cytosol protein) and are included in these analyses, because of increasing use of immunohistochemistry during the final years of accrual to the trial.

IBCSG Trial VII investigated the value of adding chemotherapy to tamoxifen among patients with lymph node-positive disease. From 1986 to 1993, 1212 eligible postmenopausal patients with node-positive disease were randomized to receive one of four treatments: tamoxifen alone for five years; tamoxifen plus three courses of ''classical'' CMF in months 1, 2, and 3; tamoxifen plus three delayed courses of CMF in months 9, 12, and 15; or tamoxifen plus both early and delayed CMF.[11] Tamoxifen was given concurrently with the chemotherapy and was administered for a duration of five years in all treatment groups. The randomization was prospectively stratified by the ER status of the primary tumor. Approximately 95% of trial patients had ER and PgR measured by an extractive assay and are included in these analyses.

To explore the trends in treatment effect differences according to hormone receptor levels

(based on extractive assays), we used the nonparametric Subpopulation Treatment Effect Pattern Plot (STEPP) methodology.[6–8] STEPP involves defining several overlapping subgroups of patients on the basis of a covariate of interest and studying the resulting pattern of the treatment effects estimated within each subpopulation. Here, ER and PgR were the covariates of interest. For a STEPP analysis, the subpopulations contained a fixed number of patients and each subpopulation was formed by moving left to right by dropping approximately 10–15 patients with the lowest covariate value and adding approximately 10–15 with the next higher covariate value. The *x*-axis indicated the median covariate value (ER or PgR on the log-scale) for patients in each subpopulation; the *y*-axis indicated the five-year disease-free survival (DFS) percentage estimated using the Kaplan-Meier method on data of patients in each subpopulation.

Five-year DFS percentages were estimated with the Kaplan-Meier method and Greenwood's formula was used for the calculation of standard errors. Hazard ratios (RR) and confidence intervals were estimated by using a proportional hazards model.

Results

IBCSG Trial IX

We reported previously,[10] at a median follow-up of six years, that CMF followed by tamoxifen significantly improved DFS compared with tamoxifen alone (RR = 0.80; 95% CI 0.64–1.00). However, the effectiveness of adding CMF to the adjuvant treatment regimen was observed exclusively among patients with ER-negative disease (RR = 0.52, 95% CI 0.34–0.79); no treatment difference was observed for patients with ER-positive tumors (RR = 0.99; 95% CI 0.75–1.30). A recent reanalysis of the NSABP B-20 study confirmed the absence of benefit of adding chemotherapy to tamoxifen for postmenopausal women with lymph node-negative, ER-positive breast cancer.[12]

Figure 1A shows the STEPP analysis of five-year DFS according to quantitative values of ER for IBCSG Trial IX; each subpopulation contains approximately 200 patients and changes by approximately 15 patients. The large benefit of adding CMF prior to commencing tamoxifen is clearly evident for the lowest values of ER. In particular, when CMF is given sequentially prior to tamoxifen among patients with tumors expressing no ER, the five-year DFS is improved from 67% without CMF to 85% with CMF ($n = 20$ and 26, respectively). For values of ER exceeding 9 fmol/mg cytosol protein, no benefit of added CMF is observed for any of the subpopulations defined in the STEPP analysis.

IBCSG Trial VII

We previously reported a detrimental effect of late initiation of CMF at 9, 12, and 15 months concurrent with tamoxifen that had been initiated nine months earlier.[7,11] 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.[13] Median follow-up was ten years.

Figures 1B–D show the STEPP analyses according to ER for the three pairwise comparisons of CMF added to tamoxifen versus tamoxifen alone; each subpopulation contains approximately 120 patients and changes by approximately 10 patients. The patterns of CMF treatment effect according to ER are very different for Trial VII (node-positive, concurrent CMF and tamoxifen) compared with Trial IX (node-negative, sequential CMF followed by tamoxifen). Specifically, little benefit of the CMF is observed for patients with the lowest values of ER expression. This is quite noteworthy considering the large CMF benefit observed in Trial IX for low values of ER expression, as well as the effect of a single cycle of perioperative CMF observed for postmenopausal women with node-negative, ER-negative disease in IBCSG Trial V.[3]

As the ER values move into an intermediate range, the effects of adding CMF together with tamoxifen become sizeable. The five-year DFS percentages for the tamoxifen alone arm increase compared with the low expression values of ER, but those for each of the three arms that include CMF increase more rapidly. When the ER expression values are quite high, the five-year DFS achieved by tamoxifen alone reaches the level achieved by the CMF-containing arms. Thus, a pattern emerges for postmenopausal patients with node-positive disease: with low values of ER, chemotherapy given together with tamoxifen makes no substantial impact; high values of ER indicate that tamoxifen alone is a potent treatment, leaving little opportunity for CMF to contribute added benefit; intermediate values of ER indicate an opportunity for CMF to add to the benefit of tamoxifen.

Exploratory analyses incorporating PgR

One explanation for the different patterns of response according level of ER expression (especially

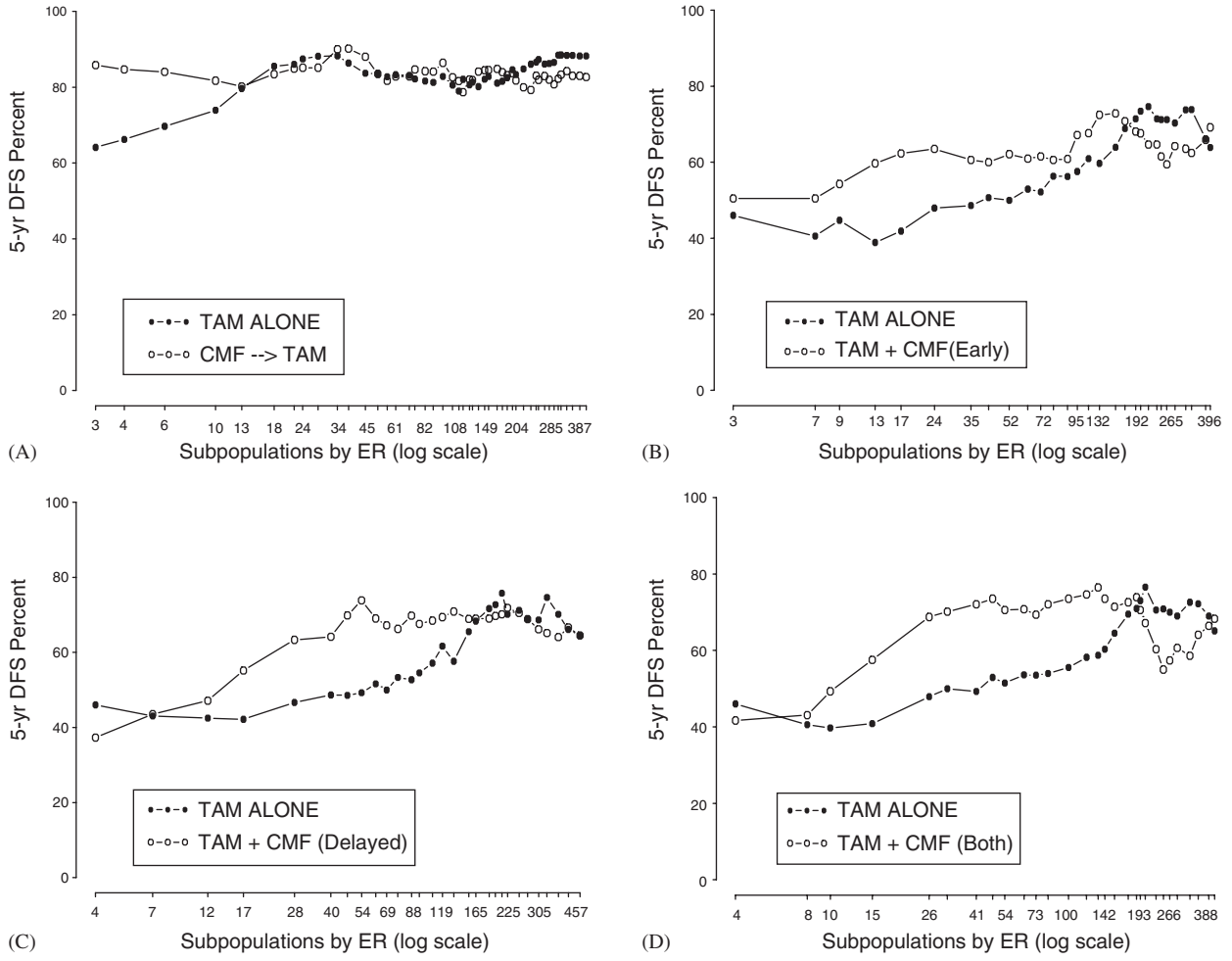

Figure 1 Subpopulation Treatment Effect Pattern Plots (STEPP) analyses of five-year DFS (%) according to quantitative ER values (fmol/mg cytosol protein) of the primary tumor. Comparison of: (A) CMF followed by tamoxifen versus tamoxifen alone in Trial IX; (B) early CMF plus tamoxifen versus tamoxifen alone in Trial VII; (C) delayed CMF plus tamoxifen versus tamoxifen alone in Trial VII; (D) early plus delayed CMF plus tamoxifen versus tamoxifen alone in Trial VII. Numbers on the *x*-axis refer to the median value of ER (fmol/mg cytosol protein) for each of the overlapping subpopulations. (Adapted from Colleoni et al.[13] with permission.)

for the node-positive Trial VII) is that tamoxifen alone is not as potent for patients with intermediate ER levels as it is for high levels of ER expression. Another explanation, however, is that intermediate ER levels indicate the presence of chemosensitive targets within the tumor. As one possibility, we investigated the relationship between ER and PgR degree of positivity. Using cut-offs suggested from the STEPP analysis of ER level, ER was divided into three groups (ER <10, 10–99, and $\geqslant 100$ fmol/mg cytosol protein). Within each of these groups we undertook STEPP analyses for PgR expression; in addition, we summarized outcome among two PgR groups (PgR <10 and PgR $\geqslant 10$ fmol/mg cytosol protein). Two rather than three PgR groups were considered and the three CMF-containing groups in Trial VII were combined because of sample size limitations.

Table 1 shows results with respect to DFS for different groups defined by ER and PgR expression in Trials IX and VII. For the node-negative Trial IX, 71% of patients with intermediate ER levels had PgR $\geqslant 10$ fmol/mg cytosol protein, compared with 58% for the node-positive Trial VII. In general, more heterogeneity of PgR expression within cohorts defined as ER-positive (i.e., intermediate or high) was observed for women with node-positive compared with node-negative disease.

For Trial IX, STEPP analyses reveal that PgR did not appear to influence the degree of response to CMF over and above that defined according to ER category (Fig. 2). Among the groups summarized in Table 1, CMF response among patients with ER 0–9 fmol/mg cytosol protein tumors was observed regardless of PgR level; no effect was observed for

Table 1 Disease-free survival (DFS) outcome according to estrogen receptor (ER) and progesterone receptor (PgR) cohorts for IBCSG Trial IX (node-negative, postmenopausal) and IBCSG Trial VII (node-positive, postmenopausal)

ER; PgR cohorts (fmol/mg cytosol protein)	Treatment	Events/patients	Five-year DFS% ± SE	HR (95% CI)
Trial IX (node-negative)				
ER: 0–9; PgR: 0–9	CMF → Tam	22/102	82.8 ± 3.8	0.56 (0.33–0.94)
	Tam	39/112	65.7 ± 4.8	
ER: 0–9; PgR: ⩾10	CMF → Tam	4/35	88.6 ± 5.4	0.28 (0.09–0.88)
	Tam	12/35	64.6 ± 8.8	
ER: 10–99; PgR: 0–9	CMF → Tam	10/65	84.5 ± 5.1	0.55 (0.25–1.22)
	Tam	17/62	76.9 ± 5.7	
ER: 10–99; PgR: ⩾10	CMF → Tam	28/142	83.1 ± 3.5	1.32 (0.76–2.27)
	Tam	24/166	87.1 ± 2.9	
ER: ⩾100; PgR: 0–9	CMF → Tam	11/31	71.7 ± 8.7	1.19 (0.51–2.76)
	Tam	11/37	79.1 ± 7.1	
ER: ⩾100; PgR: ⩾10	CMF → Tam	37/193	85.9 ± 2.7	0.98 (0.61–1.57)
	Tam	33/179	85.8 ± 2.8	
Trial VII (node–positive)				
ER: 0–9; PgR: 0–9	CMF+Tam	111/163	44.1 ± 3.9	0.91 (0.63–1.34)
	Tam	35/50	44.0 ± 7.0	
ER: 0–9; PgR: ⩾10	CMF+Tam	24/34	41.2 ± 8.4	1.78 (0.73–4.38)
	Tam	6/11	63.6 ± 14.5	
ER: 10–99; PgR: 0–9	CMF+Tam	67/107	59.8 ± 4.7	0.67 (0.44–1.01)
	Tam	35/47	42.6 ± 7.2	
ER: 10–99; PgR: ⩾10	CMF+Tam	91/154	71.3 ± 3.7	0.79 (0.53–1.17)
	Tam	35/56	51.8 ± 6.7	
ER: ⩾100; PgR: 0–9	CMF+Tam	44/60	51.7 ± 6.5	1.27 (0.69–2.37)
	Tam	13/20	65.0 ± 10.7	
ER: ⩾100; PgR: ⩾10	CMF+Tam	186/346	71.8 ± 2.4	0.76 (0.57–1.00)
	Tam	68/105	66.7 ± 4.6	

the ER-positive groups, though small sample sizes in the ER-positive/PgR 0–9 groups limit conclusions.

For Trial VII (Fig. 3), the STEPP analysis among low ER group suggests that PgR-absent and very low PgR benefit from adjuvant CMF; note that this is not evident from the data for ER 0–9 in Table 1. Among the intermediate ER group, again low PgR suggests benefit from CMF, but a benefit may be sustained regardless of PgR level. Finally, among the ER-high group the treatment difference reverses, wherein no benefit of CMF is observed at low PgR values, and some benefit appears at higher PgR values.

These analyses are exploratory and should be used to motivate assessments in other datasets to confirm or refute the role of PgR (as well as other factors) to predict response to chemotherapy within cohorts of ER-positive disease.

Age is not a therapeutic target

The analyses of IBCSG Trials IX and VII, as well as other results from clinical trials, suggest that the magnitude of chemotherapy effectiveness would be better estimated by considering primarily the ER level—and possibly the PgR level—of the primary tumor and the potential confounding associated with use of tamoxifen. By contrast, the results of the EBCTCG Overview[14] are presented primarily according to age: chemotherapy demonstrated substantial effectiveness in women below the age of 50 years, but only a modest effect for women aged 50–69. In fact, EBCTCG results for ER-poor tumors in the absence of tamoxifen show substantial benefit of chemotherapy compared with no chemotherapy, irrespective of age (EBCTCG 2000 Update, personal communication). Including tamoxifen-confounded trials substantially reduces the observed chemotherapy effectiveness for the ER-poor cohort among patients 50–69 years of age. For patients with ER-positive tumors, chemotherapy with tamoxifen provides substantial benefit compared with tamoxifen alone for women <50 years old, but the magnitude of benefit is not as substantial for women $\geqslant 50$ years.

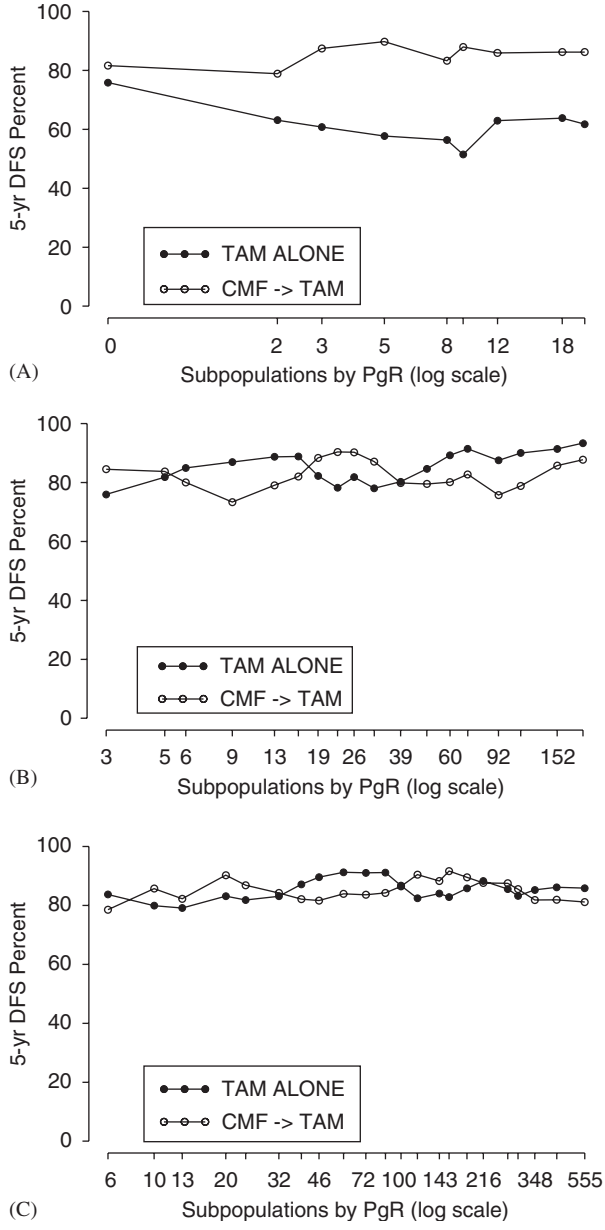

Figure 2 STEPP analyses of five-year DFS (%) according to quantitative PgR values (fmol/mg cytosol protein) in the primary tumor, comparing CMF followed by tamoxifen versus tamoxifen alone in IBCSG Trial IX. Cohorts of patients whose tumors contained ER in levels of: (A) 0–9 fmol/mg cytosol protein; (B) 10–99 fmol/mg cytosol protein; (C) $\geqslant$100 fmol/mg cytosol protein. Numbers on the *x*-axis refer to the median value of PgR (fmol/mg cytosol protein) for each of the overlapping subpopulations. NB: the *x*-axes for these plots cover different ranges of PgR values reflecting the correlation between quantitative ER and PgR levels.

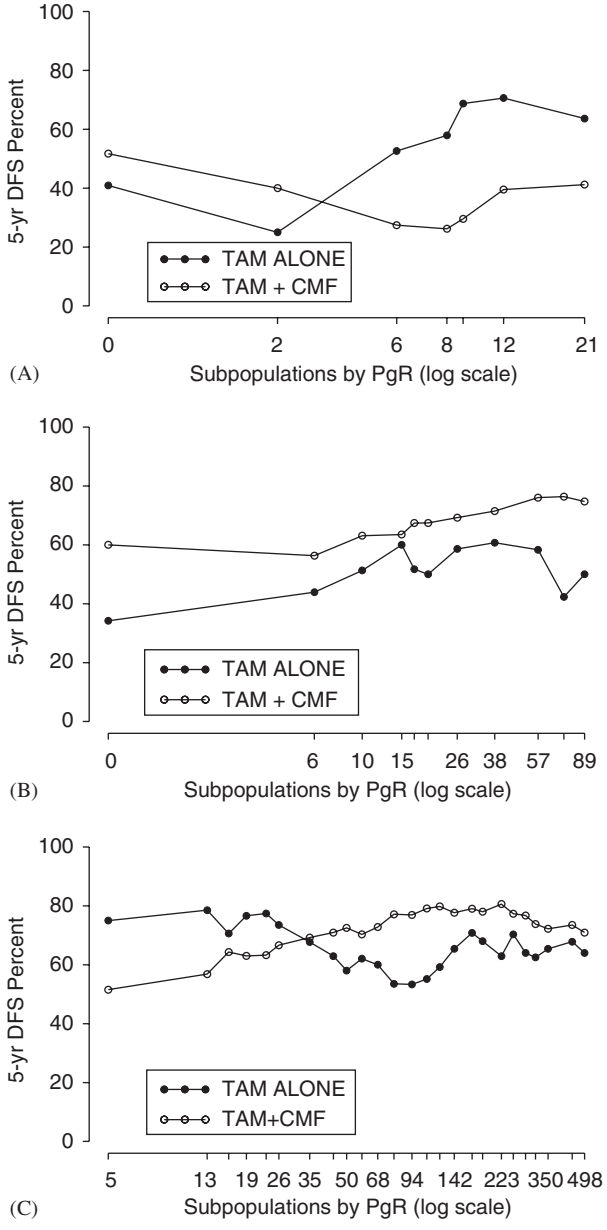

Figure 3 STEPP analyses of five-year DFS (%) according to quantitative PgR values (fmol/mg cytosol protein) in the primary tumor, comparing concurrent CMF and tamoxifen versus tamoxifen alone in IBCSG Trial VII. Cohorts of patients whose tumors contained ER in levels of: (A) 0–9 fmol/mg cytosol protein; (B) 10–99 fmol/mg cytosol protein; (C) $\geqslant$100 fmol/mg cytosol protein. Numbers on the *x*-axis refer to the median value of PgR (fmol/mg cytosol protein) for each of the overlapping subpopulations. NB: the *x*-axis for these plots cover different ranges of PgR values reflecting the correlation between quantitative ER and PgR levels.

Discussion

Recent results, in addition to those from the IBCSG trials presented above, emphasize the need to explore clinical trial data primarily with respect to treatment effects within cohorts defined by steroid hormone receptor status of the primary tumor. Albain et al.[15] reported an exploratory analysis of

SWOG/Intergroup Trial 0100, which compared CAF plus tamoxifen (either concurrent or sequential) with tamoxifen alone for postmenopausal women with node-positive, receptor-positive breast cancer. Results of treatment comparisons conducted separately for low/intermediate ER levels and for high ER levels were identical to those of IBCSG Trial VII; adding CAF to tamoxifen provided benefit compared with tamoxifen alone for the low/intermediate ER cohort, but not for the patients with high levels of ER (interaction $P = 0.046$).[15]

Another evaluation of response to chemotherapy by endocrine responsiveness was performed for three CALGB/Intergroup trials, all of which had a more "intensive" compared with "standard dose" chemotherapy. While the overall result of each trial showed a significant benefit for the experimental treatment regimen (typically more intense) and in the subgroups classified as ER-negative (in the latter described as overwhelming), the difference between the two treatment arms was negligible in patients considered to have ER-positive cancers (most of whom also received tamoxifen prescribed for five years as part of their adjuvant treatment program).[16] The effectiveness of chemotherapy when unconfounded with endocrine therapy is substantial for patients with endocrine nonresponsive breast cancer. This phenomenon was described initially over a quarter of a century ago.[17]

For patients with endocrine-responsive breast cancer, endocrine therapies should be the mainstay of the adjuvant systemic treatment regimen: tamoxifen and/or aromatase inhibitors for postmenopausal women, tamoxifen and/or ovarian function suppression/ablation for premenopausal women. Despite evidence of endocrine responsiveness based on ER status of the primary tumor, some women benefit from the addition of cytotoxics together with or prior to endocrine therapy. From IBCSG VII, women with intermediate levels of ER in their tumors benefited substantially from concurrent administration of CMF and tamoxifen even when the CMF administration was initiated several months following the start of tamoxifen. The benefit was observed especially in tumors with intermediate ER, but low levels of PgR. Also, in the SWOG/Intergroup Trial 0100,[15] women with tumors having low/intermediate levels of ER benefited similarly from the addition of CAF, whether concurrent or sequential.

In contrast to the node-positive population, postmenopausal women with node-negative, endocrine-responsive tumors did not benefit in terms of disease-free survival from the addition of chemotherapy to tamoxifen. This was seen in both the IBCSG Trial IX[10] in the population of women 60 years of age and in NSABP B-20.[12]

The recent report by Roché et al.[18] further illustrates the need to develop and test hypotheses considering the complexity of cytotoxic and endocrine-mediated effects of adjuvant therapies. The PACS 01 Trial conducted in France and Belgium found that a regimen of three courses of FEC followed by three courses of docetaxel was superior to six courses of FEC for women 50 years of age or more with node-positive disease, but no difference was seen for women less than 50 years old. Approximately three-quarters of the patients had ER- or PgR-positive tumors, suggesting that endocrine mechanisms should be considered to interpret the results. The use of high doses of methylprednisolone as prophylactic corticotherapy with docetaxel might reduce estrogen levels produced by the adrenals in postmenopausal women, thus contributing to the observed effect in this age cohort. The 21-year update of IBCSG Trial IV[19] continued to show a highly significant advantage favoring continuous low-dose prednisone plus tamoxifen administered for one year compared with no adjuvant therapy for patients 66–80 years of age. A re-assessment of the taxane trials focusing on postmenopausal patients with endocrine-responsive disease is recommended.

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 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 levels of expression (ER- or PgR-positive).

These features should be considered both for the care of patients today and for the interpretation of results of clinical trials that were conducted and reported in the past.

Conclusions

It is clear that improved tailoring of available therapies is a prerequisite to continued progress in the adjuvant breast cancer setting. Exploration of data according to endocrine responsiveness is the

first step to better tailoring of therapies. The additional definition of chemosensitive targets and the use of new biologics are especially required for patients with tumors in the intermediate endocrine-responsive range.

Acknowledgements and sources of support

We thank the patients, investigators, nurses, data managers, and all others who participate in the IBCSG trials (see Appendix A for participants and authors). We specifically acknowledge the contributions of Marco Bonetti, Monica Castiglione-Gertsch, Alan Coates, Marco Colleoni, Shari Gelber, Aron Goldhirsch, and Karen Price. We acknowledge the initial support for IBCSG provided by the Ludwig Institute for Cancer Research, the Cancer League of Ticino, and the Swiss Cancer League, and the continuing support for central coordination, data management, and statistics provided by the Swedish Cancer Society, the Cancer Council Australia, the Australian New Zealand Breast Cancer Trials Group (NHMRC Grant Numbers 880513, 910420, 890028, 920876, 950328, 980379), the Frontier Science and Technology Research Foundation, the Swiss Group for Clinical Cancer Research, the United States National Cancer Institute (CA-06516 and CA-75362), and the American-Italian Cancer Foundation (AICF 101-98 and 101-99).

Appendix A. International Breast Cancer Study Group (IBCSG) Trials VII and IX: Participants and authors

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