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8. INNOVATIVE STRATEGIES OF ADJUVANT TREATMENTS

Features that predict responsiveness to chemotherapy and endocrine therapies

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SUMMARY. Prognostic factors, characterizing the background level of risk of relapse, and predictive factors, characterizing the degree of responsiveness to a specific treatment, are both used to select adjuvant therapies for patients with early-stage breast cancer. Determining how best to utilize available factors is challenging. We review various prognostic and predictive factors and present examples to illustrate how these factors can be used to improve our understanding about selection of adjuvant treatments, re-evaluation of data from previous clinical trials and design of future studies. Steroid-hormone-receptor status of the primary tumour and patient age/menopausal status (primarily reflecting the robustness of ovarian function) are the key features that predict responsiveness to chemotherapy and endocrine therapies. Qualitative interactions between these factors, and effects of combining chemotherapy and endocrine therapies, may confound treatment comparison. The STEPP (Subpopulation Treatment Effect Pattern Plots) method, by investigating the patterns of treatment effects within randomized clinical trials or datasets from meta-analyses, will help to identify features that predict responsiveness to the treatments under study without the pitfalls of selective retrospective subset analysis. Subset analyses according to steroid-hormone-receptor status and patient age should now be considered as prospectively defined. Future clinical trials should be designed as tailored treatment investigations, with endocrine therapies being evaluated within populations of patients with endocrine-responsive tumours, and chemotherapy questions being addressed within populations of patients with endocrine non-responsive disease. © 2001 Harcourt Publishers Ltd

INTRODUCTION

Although the terms, prognostic factors and predictive factors, are in common usage, there remains some confusion about their distinction. *Prognostic factors* are characteristics of the patient or the tumour that are useful for discriminating baseline prognosis. They are useful for defining the background level of risk of relapse against which the benefits and burdens of adjuvant therapies can be weighed. Case series in which risk of relapse is correlated with level of the feature may be sufficient to identify prognostic factors. *Predictive factors* are characteristics of the patient or the disease that are useful to predict the magnitude of response or the degree of resistance to a given treatment. Predictive factors are inextricably linked to the specific treatment for which responsiveness is defined and are therefore critical for eventually defining tailored treatment approaches for subpopulations of patients. Identification of features that predict responsiveness to therapy must be accurate, reliable and reproducible, but several practicalities impede progress. Only randomized clinical trials can provide reliable, evidence on prediction of response because estimates of the magnitude of treatment effect compared with a control group are required. The precise identification of a predictive factor (i.e. detection of an interaction between the value of

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Table 1 Potential prognostic and predictive factors

Tumour-related factors	Patient-related factors	Treatment-related factors
ER and/or PgR status	Age	Timing
HER2/neu c-erbB2	Menopausal status	Duration
Axillary nodal status	Ethnicity or race	Agents
Histology	Socioeconomic status	Schedule
pT size	Treatment within trials	Endocrine effects of chemotherapy
Grade	Co-morbid conditions	Interaction between treatments
Proliferation: Ki67/EIC	Additional medication	(chemotherapy and tamoxifen)
Clear margins		
EGF and R		
P53		
bcl 2		
BRCA1/BRCA2		
Several others:		
MLH1 (MMR)		
Bcar1/p130Cas		
Proteinase inhibitor		

the factor and the magnitude of treatment effect) requires four times the number of events as to detect a main treatment effect. Furthermore, qualitative interactions involving several factors and treatment combinations considered simultaneously have been identified in breast cancer. It is not surprising, therefore, that relatively few predictive factors have been identified that are currently useful for selecting adjuvant therapies.

To predict response we must focus on tumour-related factors, patient-related factors, and treatment-related factors and investigate how all of these interact. Table 1 lists several factors that have been considered for their prognostic and predictive potential. Of these, only steroid-hormone-receptor status of the primary tumour and patient age/menopausal status have relevance today as predictive factors in the adjuvant setting. HER2/neu status is likely to become important if ongoing studies of trastuzumab yield positive results. Several treatment-related features must also be considered including timing, duration, type of agents, schedule, endocrine effects of chemotherapy and the interaction between treatments (e.g. concurrent chemotherapy and tamoxifen). As chemotherapy (anthracycline-based or not), tamoxifen, ovarian function suppression, and radiation therapy have all been demonstrated to be effective treatments in overview analyses, a current acute challenge is to determine how best to utilize these available therapies to improve patient care. The key to meeting this challenge is the selection and integration of relevant evidence concerning the magnitude of treatment effect.

METHODS

In this paper we present several examples illustrating how currently available predictive factors can be used to improve our understanding about selection of adjuvant treatments, re-evaluation of data from previous clinical trials and design of future studies. These examples rely on subset analyses according to the two most important factors – steroid-hormone-receptor status of the primary tumour and patient age/menopausal status (primarily reflecting the robustness of ovarian function). We also present several applications of the STEPP (Subpopulation Treatment Effect Pattern Plots) method to illustrate how investigating the patterns of treatment effects within randomized clinical trials or datasets from meta-analyses helps to identify features that predict responsiveness to the treatments under study without some of the pitfalls of selective retrospective subset analysis.

RESULTS

Endocrine effects of chemotherapy: inadequate results among very young patients with endocrine-responsive disease

Data from the International Breast Cancer Study Group (IBCSG) randomized clinical trials in premenopausal women conducted between 1978 and 1993 were published by Aebi et al.[1] 314 (8.5%) of the 3700 premenopausal patients were under 35 years-of-age at diagnosis. Among the 84% of patients with ER measured, the distribution of ER-positive and ER-negative tumours was about equal for the women under 35 (51% versus 49%), while a preponderance of tumours were ER-positive for patients 35 years-of-age and older (63% versus 37%). Patients with ER-positive tumours are presumed to have a more favourable

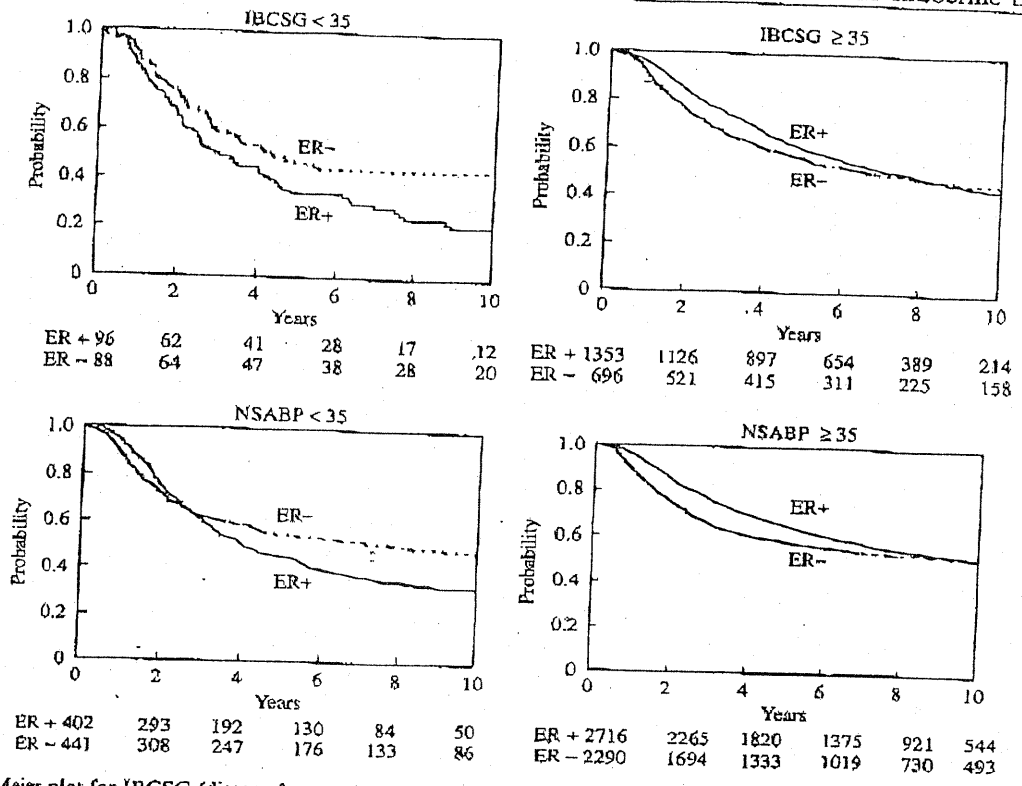

Fig. 1 Kaplan–Meier plot for IBCSG (disease-free survival for 2233 premenopausal patients) and NSABP (relapse-free interval for 5849 women under 50 years-of-age at diagnosis) according to ER-status and age at diagnosis (reprinted with permission of Oxford University Press[2]).

prognosis than patients with ER-negative tumours. However, the retrospective subgroup analysis found that for patients less than 35 years-of-age at diagnosis, the ER-positive cohort did very poorly, and in fact significantly worse than patients with ER-negative tumours. For patients 35 years of age or older, the opposite was found: those with ER-positive tumours did better than those with ER-negative disease.

The Kaplan–Meier curves for disease-free survival based on the 2233 patients who received at least three courses of adjuvant chemotherapy alone (classical CMF) are shown in Figure 1. The interaction between age-group and ER status was statistically significant ($P = 0.009$) indicating a striking difference in outcome according to age between the ER-negative cohort (almost no difference in outcome) and the ER-positive cohort (a big difference in outcome according to age-group, with older women doing much better than younger).[2] Because these results for very young premenopausal women were based on a retrospective data analysis on only one set of data, independent confirmation is required. US cooperative groups were therefore invited to conduct a similar analysis on their datasets in which premenopausal women received chemotherapy alone – NSABP, ECOG and SWOG participated in the collaboration.[2]

Evaluations conducted by each of the groups confirmed the findings of the IBCSG hypothesis-generating analysis; women under 35 years-of-age with ER-positive tumours had a very poor outcome (worse than patients with ER-negative tumours) if treated with chemotherapy alone. Results for ER-positive tumours were better than for ER-negative tumours among patients 35 years-of-age or older at diagnosis. Figure 1 shows the relapse-free survival analysis based on 5849 patients under 50 years old who were treated with chemotherapy alone in NSABP trials. The results from SWOG and ECOG show the same pattern.

Clearly, the outcome for young patients with ER-positive disease treated with chemotherapy alone is not very good. The addition of effective endocrine treatments for this patient population may lead to important improvements in outcome. Because there are so few patients under 35 years-of-age, these women in the past have received chemotherapy based on results obtained from the overall premenopausal population – most of

whom are in their forties. But is there an advantage for chemotherapy in the very young patients? To answer this question, a randomized clinical trial is needed.

Fortunately, the NSABP conducted Trial B-13 that compared chemotherapy (MF: methotrexate followed by fluorouracil) versus no adjuvant treatment for women with node-negative, ER-negative breast cancer. Patients less than 35 years old (16% of total) had the same magnitude of benefit from the chemotherapy (relative risk (RR) (95% CI) = 0.62 (0.29–1.3)) as those 35 years old and older (RR (95% CI) = 0.62 (0.42–0.91)), a 38% reduction in the risk of relapse in both age-groups. Thus, for ER-negative tumours, chemotherapy is very effective regardless of age. Because chemotherapy was adopted across the board for almost all premenopausal women before assaying for ER became routine, there are virtually no data available to assess the role of chemotherapy alone among very young premenopausal women with ER-positive tumours. Emerging data on the effectiveness of ovarian function suppression plus tamoxifen suggest, however, that the role of chemotherapy in very young women with endocrine-responsive tumours should be re-evaluated.[3,4]

To subset or not to subset: two examples

Statisticians often caution against conducting retrospective subset analyses. Such analyses have a high chance to yield apparent treatment – covariate interactions (i.e. treatment appears to be effective for one subset of patients but not for another subset), when in fact the magnitude of the treatment effect is really similar for the different subsets. For example, if the observed overall effect of treatment is significant at the $P = 0.05$ level, even if the population is randomly divided in half there is a one in three chance that the treatment effect will be highly significant ($P < 0.003$) in one half and not significant ($P \geq 0.33$) for the other half.[5] Based on real concerns about acting on spurious results, recommending treatments based on the overall results from a clinical trial and avoiding recommendations that take subset analyses into account is a reasonable approach. The difficult issue, however, is to determine when treatment decision-making based on subset analyses is likely to provide better patient care than using the overall average result to guide treatment across the board. Two examples are presented to illustrate the issue: one relying primarily on a subset analysis and the other relying primarily on the overall result.

Since 1984, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has been conducting overview analyses (meta-analyses) of randomized clinical trials, investigating whether various forms of adjuvant therapy for breast cancer are effective. A guiding principle of these analyses has been to focus on overall results rather than on subsets, even when independent evidence suggests that subgroup differences exist.[6] Nevertheless, the recent tamoxifen overview focuses on estimates of the magnitude of the tamoxifen effect based on 8000 (17%) of the total 48 000 patients randomized in trials comparing tamoxifen versus no tamoxifen; only patients with ER-positive tumours who were enrolled in trials evaluating tamoxifen durations of at least 5 years are included.[7] The subset is justified on the basis that this is the group and duration most relevant for use of tamoxifen today. Previous analyses based on grouping patients according to age rather than according to ER status indicated that tamoxifen provided little benefit for young women.[8] Even in the past, the arithmetic construction of the overview analyses served to obscure detection of treatment effects for patient subpopulations.[9]

In contrast to the recent tamoxifen overview, now properly focused on a relevant patient population that received an appropriate treatment duration, the Intergroup Trial (lead by the CALGB), assessing the role of Taxol following four cycles of AC chemotherapy, focused its conclusions exclusively on the overall results, dismissing evidence of different magnitudes of treatment effectiveness according to subgroups. This trial used a 3×2 factorial design to evaluate three doses of doxorubicin in the AC regimen with or without an additional four cycles of Taxol. 3121 patients were enrolled. The study was first reported at ASCO in May 1998 at 20 months of median follow-up.[10] There was no difference according to dose of anthracycline, but a statistically significant reduction in the risk of relapse (HR = 0,78) was observed for the Taxol group based on the entire study population. Little attention was given to the subset analysis according to ER status of the primary in which almost all of the benefit of adding Taxol derived from the 1055 patients (34%) with ER-negative tumuors. Updated results at 30 months median follow-up were presented in April 1999 (HR = 0.78), and at 52 months median follow-up at the US NIH Consensus development conference in November 2000 (HR = 0.87). At each update, the magnitude of the statistically significant benefit of adding Taxol was sustained for patients with ER-negative tumours. In contrast, the benefit for the patients with ER-positive tumours never achieved statistical significance and in fact the estimated effect of adding Taxol was nil (HR = 1.00) at the most recent evaluation. Patients with ER-negative tumors are known to have a high risk of early relapse (within 2–3 years), while those with ER-positive

tumours experience a more protracted time-to-relapse. In the CALGB study, therefore, early results were dominated by treatment effects arising from the ER-negative cohort. The reduced overall efficacy of Taxol at the recent update of this trial could be expected as the relative number of events contributed by the ER-positive cohort increases. The key question is whether the overall average estimated treatment effect of Taxol is relevant for defining therapy for individual patients. The evidence today clearly suggests that it is not. The history of the CALGB study provides further support for the hypothesis that ER-negative status is a predictive factor for chemotherapy response. Estimates of chemotherapy treatment response and evaluations of chemotherapy questions (e.g. role of taxanes and timing and duration of treatment) should now be provided separately for patients with endocrine-non-responsive tumours and for those with endocrine-responsive disease.

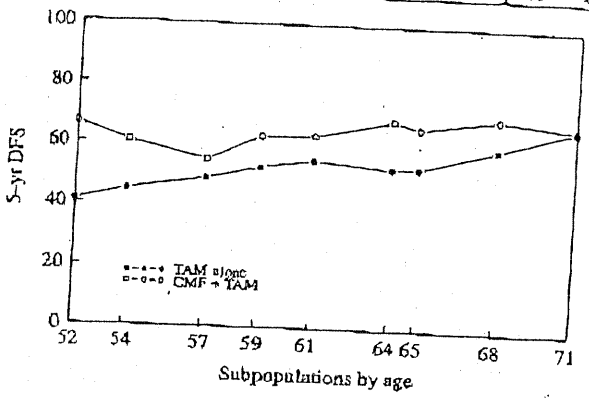

Fig. 2 STEPP plot of 5-year DFS percents for IBCSG Trial VII comparing tamoxifen alone versus tamoxifen plus early CMF according to age.

Subpopulation treatment effect pattern plots (STEPP)

As mentioned above, subset analyses are problematic. Ordinarily subset analyses are conducted to compare treatment effects according to specific cohorts of patients; for example comparing the effect of chemotherapy for postmenopausal patients less than 65 years-of-age with the effect for patients aged 65 or older. As an alternative, the STEPP (subpopulation treatment effect pattern plot) methodology was developed to examine the pattern of treatment differences across a sequence of overlapping patient subpopulations defined by a covariate of interest (e.g. age).[11,12] 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,[11] differences in means or proportions, or estimates of 5-year DFS.[12] 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.[12]

Data from the IBCSG Trial VII are used to illustrate the STEPP method.[13] IBCSG Trial VII enrolled 1212 postmenopausal patients with node-positive disease between 1986 and 1993 to evaluate tamoxifen alone, versus tamoxifen plus three courses of 'classical' CMF in months 1, 2, 3, versus tamoxifen plus three delayed courses of CMF in months 9, 12, 15, versus tamoxifen plus both early and delayed CMF. Tamoxifen was given concurrently with the chemotherapy and was administered for the duration of 5 years in all treatment groups.

Figure 2 shows a STEPP analysis of 5-year DFS percents (y-axis) for the tamoxifen alone and the tamoxifen plus early CMF treatment groups according to patient age (x-axis). The plotted points are 5-year Kaplan–Meier DFS estimates obtained from subpopulations that each include approximately 120 patients. For example, the first points on the left side of the plot are 5-year DFS percents calculated from the 92 youngest patients. The median age for this youngest subpopulation is 52 years. The points moving from left to right are obtained by sliding across the population based upon age (dropping approximately 15 cases with the lowest age and adding 15 patients with the next higher age to define the next subpopulation) and estimating 5-year DFS percents for each treatment group within each subpopulation. The values on the x-axis below the plotted points indicate the median age for the subpopulation used to obtain the 5-year DFS estimates. We previously published that the effect of adding early CMF to tamoxifen was less for patients aged 65 years or older compared with those under 65 years.[14] The STEPP analysis shows that indeed treatment differences for older patients are less than for younger. It also illustrates, however, some variability in treatment difference according to age, such that a subset analysis with age cut-off of 60 years or above might yield similar treatment benefit for older compared with younger women. The STEPP analysis also indicates that the biggest observed difference in 5-year DFS between tamoxifen alone and tamoxifen plus early CMF was obtained for patients in their early fifties. The 5-year DFS estimates shown in Figure 2 are subject to large statistical variation due to the limited number of patients evaluated in each subpopulation. Nevertheless they illustrate that distinctions in the effect of adding chemotherapy to tamoxifen according to age are not sharp.

The randomization for IBCSG Trial VII was prospectively stratified by ER-status, which had to be known at the time of study entry. The overall results at 10-years' median follow-up suggested that the addition of chemotherapy to tamoxifen might improve DFS ($P = 0.15$). However, the timing of events in the Kaplan–Meier curves indicated a different response to treatment for the ER-negative and ER-positive cohorts.[13] For the ER-positive group, DFS was improved compared with tamoxifen for all three treatments that included CMF. In contrast, for patients with ER-negative tumours, there was a more rapid decline in the DFS curves for patients in both of the two treatment groups assigned to delayed CMF. For the ER-negative cohort, this supports the hypothesis that adding tamoxifen concurrently with chemotherapy for postmenopausal patients with ER-negative tumours reduces the effectiveness of the chemotherapy.

Figure 3 shows the STEPP analysis of Trial VII comparing tamoxifen alone versus each of the three chemoendocrine therapy groups according to quantitative values of ER in the primary tumuor. Subpopulations included approximately 140 patients each and 20 cases were exchanged to define subsequent overlapping subpopulations. In each pairwise comparison; adding chemotherapy to tamoxifen improved outcome for patients with ER-positive tumours, but primarily in cases with moderate levels of positivity. For higher values of ER expression, the results for tamoxifen alone approached those for the chemoendocrine therapies. For subpopulations of patients with low or no values of ER expressed, adding CMF concurrently with tamoxifen did not provide an advantage. In fact, for both treatments that included delayed CMF, a detrimental effect of adding chemotherapy was observed in the subpopulations with the lowest values of ER. Because even the subpopulation with the smallest ER values included patients whose tumours expressed some ER, two additional estimates plotted on the left side of the STEPP plots in Figure 3 show the 5-year DFS percents for the small number of patients (approximately 20 in each treatment group) with ER-absent tumours (ER = 0 fmol/mg cytosol protein). Although the statistical variability of these estimates is quite large, they provide further support for the hypothesis that tumours not expressing steroid-hormone receptors respond differently to available adjuvant therapies than those that do have some steroid-hormone-receptor expression.

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, 1715

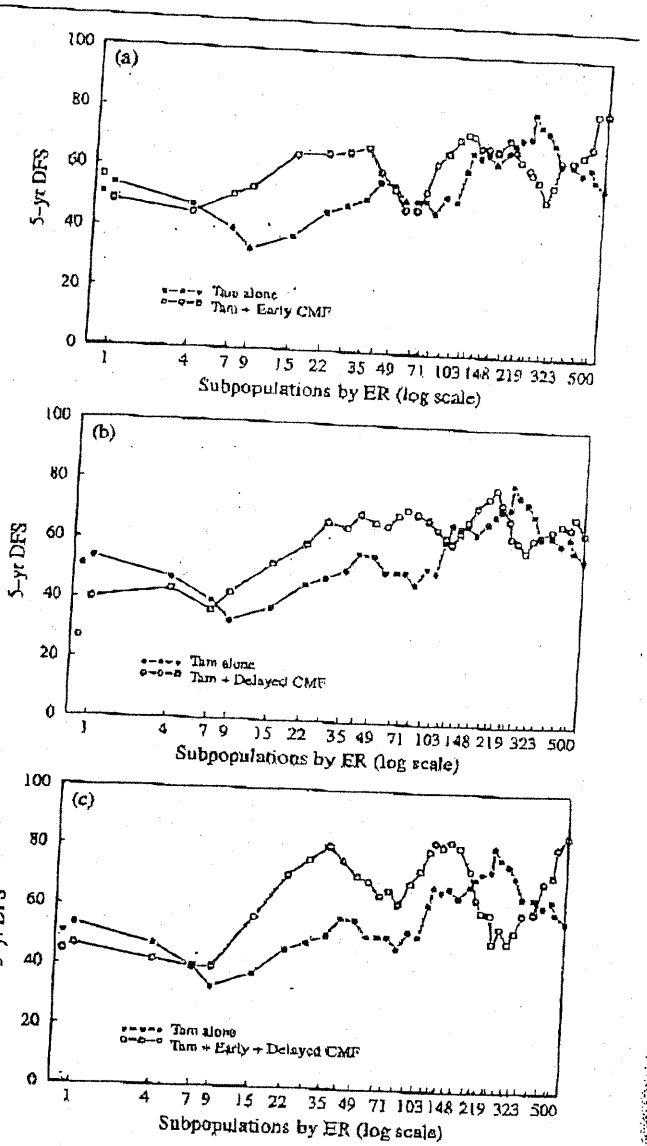

Fig. 3 STEPP plot of 5-year DFS percents for IBCSG Trial VII comparing (a) tamoxifen alone versus tamoxifen plus early CMF, (b) tamoxifen alone versus delayed CMF, and (c) tamoxifen alone versus tamoxifen plus early plus delayed CMF, according to quantitative ER values (fmol/mg cytosol protein) of the primary tumour.

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.[15] At a median follow-up of 6 years, adding CMF prior to tamoxifen significantly improved DFS ($P = 0.05$). The randomization was prospectively stratified according to ER status. A STEPP analysis of 5-year DFS for IBCSG Trial IX according to quantitative values of ER (with about 200

patients in each subpopulation) was conducted. The STEPP showed a 5-year DFS for the CMF followed by tamoxifen group of 80–85% across the entire range of subpopulations defined by quantitative ER value, while the 5-year DFS for the tamoxifen alone group was around 60–65% at low levels of ER, rising to around 80–85% for values of ER in the mid-teens and above. Thus, in contrast to Trial VII, the effect of adding CMF was seen exclusively for low values of ER, while no difference in treatment outcome was observed for values in the ER-positive range. Whether concurrent administration of chemotherapy and tamoxifen might be beneficial for postmenopausal patients (defined according to absence of ovarian function not merely according to age 50 years or greater) with ER-positive tumours awaits results of ongoing clinical trials.

DISCUSSION

A key question is whether the average effect from the entire study population is a better estimate of the magnitude of treatment benefit for an individual patient than the evaluations obtained from subpopulations defined according to potential predictive factors. We are not advocating irresponsible analyses. Statistical caveats are appropriate addenda to all analyses, and the danger of false associations arising by the play of chance needs to be considered. However, subset analyses are a matter of degree rather than an absolute rule, and such analyses conducted for confirmation of previously generated hypotheses should not be labeled as retrospective. We argue that the conservatism of refusing to entertain subset analysis is as likely to lead to harm as to good, and that ultimately false conclusions will fail to be substantiated and fall by the wayside.

The recent history of investigations of adjuvant systemic therapies for breast cancer highlights many examples suggesting differences in the magnitude of treatment effect that are sufficiently large to justify different treatment approaches for subpopulations of patients. Examples discussed in this paper include: 1) the role of chemotherapy alone for very young patients with endocrine responsive disease; 2) the important role of tamoxifen for premenopausal women defined only for the subset with ER-positive disease who receive at least 5 years of treatment; 3) the significant benefit of increased duration of chemotherapy (or perhaps addition of a taxane) exclusively for patients with ER-negative tumours who do not receive tamoxifen; 4) the detrimental effect of combined chemotherapy and tamoxifen compared with tamoxifen alone for postmenopausal patients with ER-negative tumours (similar to detrimental effects observed for receptor-negative cohorts in premenopausal age); and 5) the large benefit of short-duration chemotherapy (administered without concurrent tamoxifen) for postmenopausal women with node-negative, ER-negative disease.

New methods are required to highlight differences in the magnitude of treatment effects according to the value of a potential predictive factor. The STEPP method highlights patient subpopulations for which the average estimated effect does not accurately reflect the actual magnitude of response to a given treatment. Using STEPP to investigate the patterns of treatment effects within randomized clinical trials or datasets from meta-analyses will help to identify features that predict responsiveness to the treatments under study. Once a potential predictive factor has been postulated, its clinical relevance must be confirmed using a prospective randomized clinical trial stratified by the putative factor.

Sufficient evidence exists concerning the importance of steroid-hormone-receptor status of the primary tumour and patient age/menopausal status as predictors of response to available adjuvant systemic therapies for breast cancer. Steroid-hormone-receptor status is the key tumour-related predictive factor as it defines 'endocrine-responsive' and 'endocrine-non-responsive' cohorts. Because the efficacy of 5 years of tamoxifen has been clearly demonstrated for patients with ER-positive tumors,[7] ER status can be used to distinguish these subpopulations. The proper cut-off values of ER, the relative importance of the progesterone receptor, and the potential for endocrine non-responsive cohorts within the ER-positive population (e.g. tumours with HER-2/neu overexpression) all require further investigation.

Age/menopausal status is the key patient-related predictive factor as it is a marker for robustness of ovarian function and other endocrine-mediated pathways. Age is an important predictor of endocrine effects of chemotherapy among premenopausal patients with endocrine-responsive disease. Evidence suggests that for endocrine-responsive disease, the effects of tamoxifen are enhanced for postmenopausal patients or for premenopausal patients who have ovarian function suppression (via GnRH analogue or via chemotherapy for patients in their forties). For endocrine-non-responsive tumours, patient age has little effect on the magnitude of the treatment benefit that can be obtained from chemotherapy alone, although a slightly larger benefit might be postulated for postmenopausal women. The concurrent administration of chemotherapy and tamoxifen should be avoided for patients with endocrine-non-responsive tumours.

The above considerations concerning features that predict responsiveness to chemotherapy and endocrine therapies suggest that it is essential to revisit questions concerning the effectiveness of chemotherapy within separate cohorts defined by ER-status (surrogate for endocrine-responsive or non-responsive disease), patient age (surrogate for robustness of ovarian function) and whether or not tamoxifen (or other endocrine therapy) is given either concurrently or following chemotherapy. Datasets currently available from individual clinical trials and from meta-analyses can be used for this purpose.

For endocrine-responsive tumors, the focus for future tailored treatment investigations should be to develop even more effective endocrine treatments (e.g. new SERMS, aromatase inhibitors) and to determine how best to combine chemotherapy and endocrine treatments (or indeed to assess the benefit of adding chemotherapy to 'optimal' endocrine treatment). For endocrine-non-responsive tumours, chemotherapy questions (e.g. timing, duration, schedules and agents) unconfounded by endocrine effects and endocrine therapies, should be the focus for future tailored treatment investigations.

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