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Using Clinical Trial Data to Tailor Adjuvant Treatments for Individual Patients

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Summary

The 2005 St. Gallen Consensus Panel provided recommendations for the treatment of early breast cancer which rely on target identification first. The foremost advance since 2005— demonstration of trastuzumab efficacy for patients with HER2-positive disease—was realized because an effective treatment was being evaluated and because the trial patients had the targeted disease as determined by quality-controlled assessment prior to study entry. The BIG 1-98 trial provides a striking reminder of patients' benefit from reliable pathological tumor assessment so that targeted therapies are effectively utilized. Several statistical methods facilitate use of clinical data for individualizing treatment. Subgroup analyses summarized using forest plots are essential for better understanding the disease and its treatment. The HERA trial illustrates the interpretation of relative and absolute treatment effects and estimating hazard rates over time as means to distinguish relevant differences across subgroups. Overview analyses, joint analyses, the STEPP (Subpopulation Treatment Effect Pattern Plot) method and recursive partitioning are valuable tools.

Keywords

breast cancer; subgroup analysis; estrogen receptors; progesterone receptors; HER2; adjuvant therapy; chemotherapy; endocrine therapy; trastuzumab; STEPP

Introduction

Phase III randomized clinical trials are designed to compare two or more treatments in a large population of eligible patients. Breast cancer is a heterogeneous disease (1) and it is quite likely that different subpopulations will experience different levels and patterns of recurrence risk, and that treatment effect sizes will differ across subpopulations. Statistically the dangers associated with misinterpretation of subgroup analyses have forced clinical trialists to rely primarily on the overall treatment effect obtained from the entire trial population, avoiding any consideration of subgroups. While this “across the board” approach provides reliable evidence on the question of whether an experimental treatment works better than the control therapy on average, it provides no insight concerning potential variability of the magnitude of effect for

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heterogeneous disease and patient cohorts. Furthermore, across the board results lead to establishing a “standard” which may be applied to a broad spectrum of the patient population, thus making it impossible to conduct future research initiatives designed to tailor therapies for ‘niche’ cohorts.

Several statistical techniques are useful for bringing clinical trial data closer to the individual patient. Properly conducted and interpreted subgroup analyses are encouraged. Use of relative measures of treatment effect, absolute differences in the Kaplan-Meier estimates of disease-free survival, and hazard rates over time are illustrated. Additional approaches that help to stimulate research and highlight patient cohort differences are presented.

Target Identification

The 2005 St. Gallen Consensus Panel recognized the importance of therapeutic targets to guide the selection of adjuvant systemic therapies (2). The demonstration in 2005 of striking improvements in disease-free survival associated with the use of adjuvant trastuzumab (3,4) among patients whose tumors overexpressed HER2/neu further emphasized the importance of proper target identification (5). In fact, the use of high volume, quality-controlled, reliable and timely pathological assessment of estrogen receptor (ER), progesterone receptor (PgR) and HER2/neu status of early breast cancer could substantially improve results from adjuvant systemic therapies by assuring that proper targeted therapy is delivered to the patients who need it.

Data obtained from the Breast International Group (BIG) 1-98 study (6,7) illustrate the importance of target identification. BIG 1-98 enrolled 8010 assessable postmenopausal patients with ER- and/or PgR- positive tumors (defined according to local pathology assessment) between 1998 and 2003. Tumor specimens (blocks or slides) were available for central pathology review (conducted by Prof. Giuseppe Viale, European Institute of Oncology, Milan, Italy) for 6291 (79%) of these patients. Surprisingly, the central pathology review determined that 137 (2.2%) of the assessable cases had both ER and PgR expressed in less than 10% of cells.

Figure 1A presents the Kaplan-Meier curves for disease-free survival for BIG 1-98 according to treatment group and central pathology assessment of ER/PgR status. The hormone receptor-positive cohort (ER $\geq$ 10% and/or PgR $\geq$ 10%) experiences the pattern of recurrence observed in endocrine-responsive disease—events occur at a relatively low rate over time but continue to occur with longer follow-up—and demonstrates a meaningful difference favoring letrozole compared with tamoxifen. By contrast, the small cohort of centrally-assessed hormone receptor-negative cases (ER<10% and PgR<10%) experiences the pattern of recurrence associated with endocrine non-responsive cohorts—a high rate of early relapse with a reduced risk of relapse with longer follow-up—and benefits less from letrozole compared with tamoxifen than the group that central pathology review confirmed to have the therapeutic target. Failure of local pathology assessment to properly identify the therapeutic target led to improper adjuvant therapy recommendations for some patients who were incorrectly enrolled in BIG 1-98. Additional analyses of BIG 1-98 central pathology review findings are forthcoming (8).

Target identification is so fundamental to the success of adjuvant therapies, that the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) study includes central pathology review of tumors for HER2-positivity and for ER and PgR status prior to randomization. Only patients with HER2-positive tumors will be eligible to enroll in this 8000 patient randomized trial designed to assess the role of lapatinib alone, trastuzumab alone, their sequence and their combination. Central review of ER and PgR is intended to optimize the use of endocrine therapies for the patients enrolled in ALTTO (9).

Subgroup Analyses

The Herceptin Adjuvant (HERA) study clearly demonstrated a disease-free survival (3) and an overall survival (10) advantage for trastuzumab administered following completion of all chemotherapy among patients with HER2-positive tumors. The overall results comparing 1703 patients in the 1-year trastuzumab group with 1698 patients in the observation group showed a 36% reduction in the relative risk of a disease-free survival event ($P < 0.0001$) and a 6.3% increase in the absolute disease-free survival percentage at 3 years favoring the treated group (Figure 2A) (10). A forest plot of the hazard ratios summarizing exploratory subgroup analyses suggested treatment benefit for all evaluated subgroups (Figure 3) (10).

Cautious interpretation of retrospective subgroup analyses is required (11,12,13). This caution is justified given the high likelihood that observed differences in treatment effects according to subgroups could result from the play of chance. For example, when an overall treatment effect is statistically significant—as in the HERA study (10)—the subsequent question is not whether individual subgroups also produce a statistically significant result, but rather whether there is noticeable heterogeneity in the treatment effect with some subgroups deviating from the overall effect. To highlight this perspective, the solid vertical line in Figure 3 (10) was drawn at the overall treatment effect (hazard ratio of 0.64) rather than at the null hypothesis effect of 1.0 (12). Subgroups with confidence intervals (CIs) which fail to include the overall treatment effect are candidates for further exploration. However, failure of individual subgroups to reach statistically significant evidence against the null hypothesis of no treatment effect (i.e., CIs that include 1.0) should not be used as the basis to deny the effective treatment to some patients. For example, the age group 60 years and above in the HERA study (544 patients) did not achieve statistically significant benefit from trastuzumab while other age groups did, however the 95% CI for the older age group is quite wide and includes the treatment effect demonstrated for the overall trial population (10). Failure to achieve statistical significance should not be used to deny older patients the potential benefits of trastuzumab. Furthermore, age per se is not a therapeutic target. If there is truly less effect for older patients then it is probably due to some biological feature which is more prevalent among older than younger patients; identification and characterization of a biological feature correlated with age should be the hypothesis for future research rather than using subgroup analysis to deny effective treatment to older patients.

Completely avoiding exploration of the treatment effects according to subgroups does a disservice to both patient care and future research. In a recent editorial, Lagakos highlighted the dangers of subgroup analyses associated with multiple comparisons and the increased likelihood of false-positive claims (13). However, Lagakos also wrote, “When subgroup analyses are properly conducted, presentation of their results can be informative, especially when the treatments being compared are used in practice ... avoiding any presentation of subgroup analyses because of their history of being over interpreted is a steep price to pay for a problem that can be remedied by more responsible analysis and reporting. Ultimately, medical research and patients are best served when subgroup analyses are well planned and appropriately analyzed and when conclusions and recommendations about clinical practice are guided by the strength of the evidence.” (13) Proper conduct, reporting and interpretation of subgroup analyses can enhance rather than disturb our ability to use clinical trial data for the benefit of individual patients.

Absolute Benefits and Hazard Function Plots

From a patient care perspective, both relative treatment effects—as displayed in forest plots of hazard ratios and their CIs—and absolute treatment effects—as shown in Kaplan-Meier plots—are informative. Estimates of absolute treatment benefits within subgroups permit

evaluation of trade-offs between therapeutic burdens and benefits and are therefore important for tailoring adjuvant treatments for individual patients. For example, the relative risk reductions associated with trastuzumab in the HERA study are virtually identical for patients with node-negative [tumors had to be greater than 1 cm in size ($T>1\text{cm}$)] and node-positive disease (Figure 3; 10). A clinically relevant question is whether the absolute risk of relapse for patients with HER2-positive, node-negative disease is high enough for the relative treatment benefit of trastuzumab to provide sufficient absolute benefit. Assessment of the HERA data suggests that the absolute benefit is substantial even for the relatively lower-risk cohort with node-negative disease [$T>1\text{cm}$], as a 15% risk of relapse within 3 years of study entry was observed for this HER2-positive subgroup (RD Gelber, personnel communication).

An important but underutilized statistical technique is the presentation of hazard rates over time (14). Figure 1B presents the estimated annual hazard rates plotted over time for the patients having centrally-assessed hormone receptor-positive and hormone receptor-negative tumors regardless of treatment arm in the BIG 1-98 trial. The plot portrays the pattern of recurrence associated with hormone receptor-positive disease—events occur at a relatively low rate over time but continue to occur with longer follow-up—and that associated with hormone receptor-negative cohorts—a high rate of early relapse with a reduced risk of relapse with longer follow-up (15). Figure 2B presents the estimated hazard rates plotted over time for the observation and 1-year trastuzumab treatment groups in the HERA study (10). A substantial trastuzumab treatment benefit is seen during the early portion of follow-up with a reduction in the hazard of a disease-free survival event, and less separation between trastuzumab and observation group hazard rates with increasing follow-up (10). The relative hazard reductions according to steroid hormone receptor status are similar at 2 years of median follow-up (Figure 3;10). However, plots of the hazard functions separately for the endocrine responsive (ER-positive and/or PgR-positive) cohort and endocrine non-responsive (ER-negative/PgR-negative) cohort in the HERA study reveal fundamentally different patterns of relapse (RD Gelber, personnel communication), as observed for the BIG 1-98 trial. The endocrine non-responsive cohort has a very high early relapse risk which declines over time, and the trastuzumab effectiveness is seen during early follow-up. By contrast the endocrine responsive cohort has a lower overall risk of relapse which continues into the third year; trastuzumab reduces the risk of relapse for this cohort during all follow-up periods. Because the HERA study (as other trastuzumab trials) reached statistical significance early during follow-up, relatively few events and relatively short follow-up is available to assess the actual magnitude of trastuzumab effectiveness within subgroup. Nevertheless, it is clear that patterns of event rates are different for cohorts defined by endocrine responsiveness. Future assessments of clinical trial data should provide separate evaluations according to endocrine responsiveness and include hazard rate plots to highlight the time course of events.

Additional Statistical Methods

STEPP (Subpopulation Treatment Effect Pattern Plot)

Subgroup analyses focusing on dichotomized groups to assess differential treatment effects are associated with increased risk of false-positive findings. STEPP is an exploratory statistical method designed to assess whether the magnitude of the treatment effect observed in an overall population is consistent across subpopulations of patients distinguished according to a continuously-measured covariate of interest. STEPP analyses have been described previously and used to evaluate patterns of treatment response for breast cancer therapies (16-18).

Figure 4 illustrates a recent application of STEPP to investigate an issue relating to chemotherapy responsiveness (19). Investigators from the Danish Breast Cancer Cooperative Group (DBCG) assessed TOP2A ratio determined by FISH as the ratio between the number of gene probe signals and the number of signals for centromere 17. A total of 718 patients

randomized to either CEF (cyclophosphamide, epirubicin, 5-fluorouracil) or CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy could be evaluated. The STEPP indicates a clear superiority in favor of CEF for cohorts with low (deleted) or high (amplified) values of TOP2A ratio. While this finding is consistent with results from other series, the STEPP analysis indicated that the cut-points ordinarily used to define deletion (<0.8) or amplification (>2.0) may require adjustment for optimal selection of cohorts which obtain the most benefit from receiving an anthracycline-based chemotherapy (19).

Overview Analysis

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has published results of meta-analyses conducted using all available randomized evidence to detect a treatment effect from chemotherapy, tamoxifen, ovarian ablation/suppression and local therapies. The 2005 report on systemic adjuvant therapies re-affirms the long-standing beneficial effects of chemotherapy to reduce the risk of relapse, breast cancer mortality and overall mortality (20). The magnitude of the benefit of chemotherapy is clearly larger for younger women (those less than 50 years of age) than it is for older women (especially for women in their 60s). As age is not a therapeutic target, a recent effort was launched by the EBCTCG to assess the effects of chemotherapy among patients with tumors classified as ER-poor. The analysis demonstrates substantial and significant effects of chemotherapy obtained for patients with ER-poor tumors irrespective of patient age; the magnitude of the treatment effect for patients in their 60s was similar to that observed for women below 50 years of age (21). Exploration of biologically-motivated subgroups can provide information that is particularly relevant for the care of individual patients.

Joint Analysis

In contrast to an overview analysis, which combines data from several studies with the aim of rejecting the null hypothesis using the totality of the evidence, a joint analysis examines a research question across several studies to look for consistency. The joint analysis preserves the individual trials as separate entities, thus maintaining the opportunity to explore the individual characteristics of the trials being jointly analyzed. This approach facilitates improved understanding to enable extrapolation of findings to individual patients.

An example of joint analysis was the work of Cancer and Acute Leukemia Group B (CALGB) / North American Intergroup investigators who assessed the magnitude of the effects of various experimental chemotherapy regimens versus their respective control regimens in three consecutive CALGB trials (22). The patterns observed within the three trials were similar—the experimental chemotherapy groups (labeled ‘more intensive’ chemotherapy) each appeared to produce a larger treatment effect for patients who had ER-negative tumors (and did not receive adjuvant endocrine therapy) compared with the magnitude of treatment effect observed for patients with ER-positive tumors (most of whom received adjuvant endocrine therapy in addition to chemotherapy). Furthermore, using annualized hazard rate analysis as described above, each of the three trials showed a consistent confirmation of differences in the event rates over time for the ER-negative compared with ER-positive cohorts. The authors concluded that future trials of adjuvant chemotherapy should be designed separately for patients with ER-negative and ER-positive disease (22).

CART (Classification and Regression Tree) Analysis

CART is an alternative to multiple regression to explore which features most influence a dichotomous outcome (23). The TEXT (Tamoxifen and Exemestane Trial) is a global, phase III randomized study evaluating LHRH analogue plus tamoxifen versus LHRH analogue plus exemestane for premenopausal women with endocrine-responsive disease (24). Whether or not adjuvant chemotherapy was also given was at the discretion of physicians and patients.

CART was used to investigate which patient and disease characteristics influence whether or not chemotherapy is used among these clinical trial patients who will receive combined endocrine therapy (25). A total of 838 patients were included in the analysis, 63% of whom were offered chemotherapy. The most influential factor was lymph node status, with 87% of node-positive cases and 45% of node-negative cases receiving chemotherapy. Somewhat surprisingly, the next most influential factor was geographical region, reflecting different attitudes toward selection of chemotherapy in different parts of the world. For the node-positive cohort, chemotherapy was prescribed for 70% of patients in some geographical regions compared with 93% in other geographical regions. For node-negative cases, regional differences for chemotherapy use ranged from 31% to 60%. Other factors such as number of positive nodes, tumor size and tumor grade were also used by investigators to tailor use of chemotherapy for premenopausal women with endocrine-responsive disease. To date, for such women at lower risk of recurrence, the worth of chemotherapy when given together with LHRH analogue and tamoxifen is uncertain (26).

Conclusions

Several statistical methods are available to utilize clinical trial data to assist with tailoring adjuvant therapies for individual patients. Knowledge derived from clinical trials is already sufficient to understand that breast cancer is a highly heterogeneous disease, and that identification of therapeutic targets within individual tumors is the first step to optimize therapy. Subsequent tailoring requires information from properly conducted subgroup analyses and a consideration of both the underlying risk of disease recurrence and patient preferences that influence treatment choice.

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Figure 1.

Kaplan-Meier estimates (panel A) and annualized hazard rates with 95% CI (panel B) for disease-free survival (%) comparing letrozole versus tamoxifen among postmenopausal women in the BIG 1-98 trial, according to central pathology assessment of steroid hormone receptor status [positive = ER and/or PgR $\geq 10\%$ of cells immunoreactive; negative = ER and PgR both $< 10\%$ of cells immunoreactive]. HR(L:T) denotes hazard ratio of letrozole relative to tamoxifen; CI denotes confidence interval. Presented with permission of the BIG 1-98 Steering Committee.

Figure 2. Kaplan-Meier estimates (panel A) and annualized hazard rates (panel B) for disease-free survival (%) comparing patients assigned to receive 1 year's treatment with trastuzumab vs. observation alone in the HERA trial at 2 years of median follow up (reference 10; adapted with permission).

Figure 3.

Forest plot summarizing exploratory disease-free survival subgroup analysis comparing patients assigned to receive 1 year's treatment with trastuzumab vs. observation in the HERA trial at 2 years of median follow-up (reference 10; reproduced with permission). HR=hazard ratio; CI=confidence interval.

Figure 4. STEPP (Subpopulation Treatment Effect Pattern Plot) analysis of 10-year disease-free survival (DFS) proportion according to *TOP2A* gene ratio from the Danish Breast Cancer Cooperative Group (DBCG) Trial 89D comparing CEF versus CAF. The light lines show the 95% confidence bands for the STEPP. Presented with permission from DBCG.