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Original article

Using clinical trial data to tailor adjuvant treatments for individual patients

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Abstract

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 trial 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

1. 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 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.

2. 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

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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.

Fig. 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 $\geqslant$ 10% and/or PgR $\geqslant$ 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]

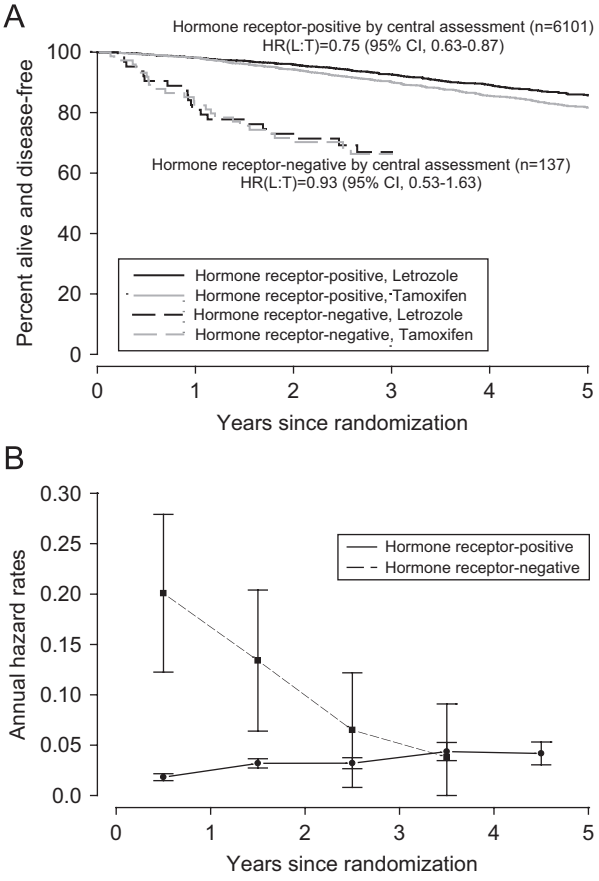

Fig. 1. Kaplan–Meier estimates (panel A) and annualized hazard rates with 95% CI (panel B) for disease-free survival (%) comparing letrozole versus tamoxifen among postmenopausal women in the BIG 1–98 trial, according to central pathology assessment of steroid hormone receptor status [positive = ER and/or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

3. 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 (Fig. 2A).[10] A forest plot of the hazard ratios summarizing exploratory subgroup analyses suggested treatment benefit for all evaluated subgroups (Fig. 3).[10]

Cautious interpretation of retrospective subgroup analyses is required.[11–13] This caution is justified given the high likelihood that observed differences in treatment effects according to subgroups could result from the play of