Statistical analysis in cancer clinical trials

Jong-Hyeon Jeong

Evidence suggests that over the long term (>5 years), tamoxifen should be replaced with an agent such as an aromatase inhibitor. Recent decisions to terminate several large clinical trials, in view of emerging efficacy data with the aromatase inhibitors, indicate that there is a need for guidelines that determine when trials should be discontinued. As a result of the interim efficacy analysis and subsequent discontinuation of the NCIC MA.17 trial, the National Surgical Adjuvant Breast and Bowel Project B-33 study was unblinded after a median of 10 months of treatment. The B-33 trial, nevertheless, demonstrated a statistically significant improvement in relapse-free survival indicating that exemestane is likely to be a valuable treatment option in postmenopausal women with early breast cancer who remain disease-free following 5 years of tamoxifen therapy. ***Anti-Cancer Drugs*** **19 (suppl 1):S9–S10 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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National Surgical Adjuvant Breast and Bowel Project Biostatistical Center, Department of Biostatistics, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Correspondence to Jong-Hyeon Jeong, National Surgical Adjuvant Breast and Bowel Project Biostatistical Center, Department of Biostatistics, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Tamoxifen, an oral selective oestrogen receptor modulator, has, until recently, been considered to be the standard endocrine adjuvant therapy for postmenopausal women with early breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 study of tamoxifen versus placebo, demonstrated that tamoxifen is effective in delaying subsequent events after removal of the original tumour within the first 5 years [1]. The B-14 data, recently reanalysed, indicate that the effect of tamoxifen increases as oestrogen receptor (ER) level increases, but this correlation fades away after 5 years (Fig. 1). This suggests that over the long term, tamoxifen needs to be replaced after 5 years with an agent such as an aromatase inhibitor (AI) that controls hormonal rather than receptor levels.

Several studies have investigated the use of an AI in patients with early breast cancer who remain disease-free following 2–3 years or 5 years of tamoxifen therapy compared with remaining on tamoxifen therapy or no further therapy. The Intergroup Exemestane Study (IES) [2] and the NSABP B-33 study [3] used different treatment strategies: in IES, patients received either tamoxifen or exemestane for 2–3 years following 2–3 years of tamoxifen; in B-33 patients were randomized to exemestane or placebo for 5 years following 5 years of tamoxifen. Disease-free survival (DFS) tends to be used fairly universally, whereas the definition of DFS varies between studies. In the IES study, the primary endpoint of DFS events includes recurrence of primary breast cancer, distant recurrence, contralateral breast cancer and death before recurrence or a secondary primary. The definition of DFS in B-33 additionally includes nonbreast secondary primaries. In NCIC MA.17 [4], the DFS events included only recurrence of primary breast cancer and contralateral breast cancer, which is similar to the definition of the relapse-free survival (RFS) endpoint in NSABP B-31 study.

Within the patient cohort, the B-33 study assumed a 50 : 50 split in terms of the nodal status. A total of 547 DFS events were required to detect a 21.3% reduction in the hazard rate with 80% power and a 5% significance level. With a targeted accrual of 3000 patients and an estimated annual accrual rate of 900, the definitive analyses were to be performed 6 years after study initiation. Planned statistical analyses initially involved a stratified log-rank test controlling for the initial pathological nodal status with a type 1 error rate of 0.05. The proportional hazards model was utilized to adjust for additional prognostic factors [5]. Secondary subgroup analyses were also to be performed if necessary.

Following the unblinding of the B-33 study, the median treatment time was 10 months in both treatment arms and the median time to crossover was also 10 months. Of a total of 783 patients receiving exemestane, 72% elected to continue treatment after unblinding whereas 9% switched to another AI. Of 779 patients receiving placebo, 44% chose to switch to exemestane and 14% to another AI. Overall, 58% of patients on placebo switched to an AI including exemestane.

Post-unblinding statistical analysis, performed at a median follow-up of 30 months [3], used an unadjusted log-rank test. The competing risks analysis based on the cumulative incidence function was used to estimate and

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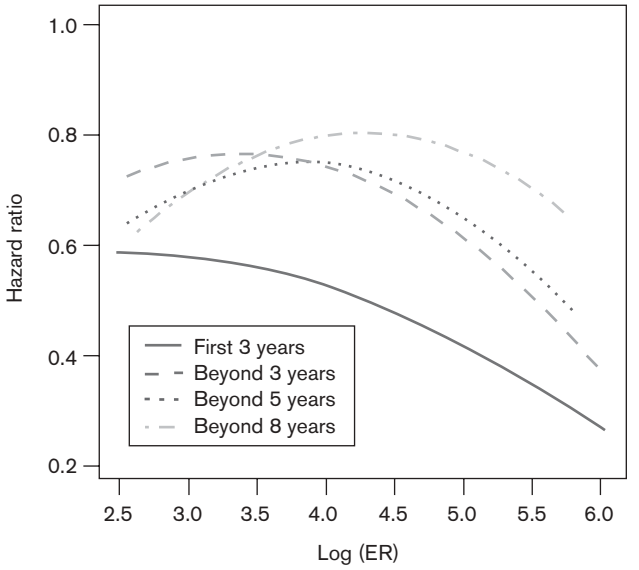
Fig. 1



Smoothed hazard ratios relative to oestrogen receptor levels for tamoxifen in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 data.

compare cumulative proportions of a subset of the DFS events over time under censoring [6].

The fact that accrual was stopped due to the results of the MA.17 trial did not generate statistical methodological problems in analysing the B-33 data. Furthermore, the B-33 study being a placebo-controlled study strengthens the findings. Several issues were, however, involved in early discontinuation of this clinical trial with regard to efficacy. As B-33 was unblinded prematurely, due to disclosure of the interim analysis results of MA.17, there were no opportunities to evaluate the long-term safety of exemestane and its effect on overall survival as well as DFS, as defined by B-33. In both B-33 and MA.17, the clinical usefulness of the data diminishes due to the short median follow-ups. As a result the NSABP B-42 study has been designed to address the duration of effect of AI therapy (i.e. 5 years versus >5 years) [7].

Recent controversial decisions to terminate several large clinical trials have highlighted the need for guidelines that determine when trials should be discontinued in view of emerging efficacy data [8–10]. The proposed guidelines suggest that trials must be allowed to continue for a preset minimum time period [10]. Furthermore, trials should not be stopped early based on measures of morbidity but only on the basis of overall mortality [8]. Buchanan and Miller [9] propose that stringent discontinuation rules should be made, which are proportional to the seriousness of the primary outcome. For example, for overall survival, current guidelines may be appropriate, but, with respect to major morbidity (e.g. DFS, RFS), no trial participant should be asked to endure a known clinically meaningful increased risk of serious morbidity. However the latter approach is statistically conservative and there is an extremely low probability of stopping a trial during the follow-up period.

In conclusion, despite early unblinding and 58% of placebo recipients switching to an AI, the B-33 trial demonstrated a statistically significant improvement in relapse-free survival [3]. Therefore, it is likely that exemestane will be a valuable treatment option in postmenopausal women with early breast cancer who remain disease-free following 5 years of tamoxifen therapy.

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