Stopping a trial early in oncology: for patients or for industry?

We read the article by Trotta et al. [1] with interest and agree that reporting of randomized controlled trials (RCTs) before meeting protocol-defined criteria for conducting a final analysis is an important and complex issue. However, we differ from some of their conclusions.

The authors analyzed 25 RCTs that were reported from 1997 to 2007 that were selected for review based on early stopping for benefit associated with experimental therapy. Two of the selected trials were conducted by the National Cancer Institute of Canada Clinical Trials Group [2, 3]. In our Pancreas.1 (PA.1) trial, we compared the novel matrix metalloproteinase inhibitor, BAY 12-9566 (experimental arm), with gemcitabine (control arm) in patients with advanced disease. However, this trial was discontinued due to inferiority not benefit of the experimental therapy [2]. As we reported, the trial design included two interim analyses, each with predefined stopping boundaries based on O’Brien-Fleming type boundaries as described by Lan and DeMets [4, 5]. These analyses were reviewed in confidence by a Data Safety Monitoring Committee (DSMC). At the second interim analysis, a predefined boundary was crossed when superior overall survival was observed in the control arm (6.59 versus 3.74 months; \(P < 0.001\); hazards ratio (HR) = 0.574, 95% confidence interval (CI) 0.445–0.740), resulting in a DSMC recommendation for trial closure. Contrary to the conclusions of Trotta et al. [1], this study exemplifies how interim analyses can detect inferior experimental treatments and prevent additional patients from being exposed to therapy less effective than standard. Further, in the case of PA.1, it would have been unethical to continue a trial of a therapy that proved significantly inferior to that of standard treatment.

In our Mammary.17 trial, 5 years of letrozole was compared with placebo in women who had completed 5 years of tamoxifen therapy for early-stage breast cancer [3]. The study protocol included two interim analyses that were to be conducted after observing one-third and two-thirds of the expected required number of events; predefined boundaries were determined as in the PA.1 trial. The trial was reported when an interim analysis conducted after observing 207 events (40% of those projected for the final analysis) was reviewed by the DSMC and showed superior 4-year disease-free survival in the experimental arm (93% versus 87%); \(P = 0.00008\); HR = 0.57, 95% CI 0.43–0.75). At this time, accrual was complete, though many patients were still receiving therapy. Following the recommendation of the DSMC, patients in the control arm who were still receiving treatment were offered therapy with letrozole. Updated analyses based on the intention-to-treat principle, and thus including substantial contamination with 66% of control arm patients receiving experimental therapy, have demonstrated sustained benefits of letrozole [6]. Therefore, we disagree with the authors’ conclusion that ‘only untruncated trials can provide the full level of evidence’, as applying principles that are methodologically sound may justify stopping a trial early when large magnitudes of benefit have been observed and the trial hypothesis adequately tested.

Finally, the authors conclude that the increasing number of trials discontinued early for benefit in the past 3 years, compared with the preceding 7 years may be market driven. While the potential influence of commercial interests should not be discounted, other reasons may include potential therapeutic advances associated with targeted therapies and sounder application of methodological principles, including larger initial sample sizes calculated to detect smaller differences and appropriate use of statistical principles in conducting interim analyses. While closure of a trial before obtaining definitive results must be avoided, there are instances where early stopping for benefit is appropriate. As Trotta et al. [1] state, and as we have previously indicated [7], establishing reporting standards for interim analyses would aid critical appraisal of trials reported before meeting projected closure criteria.

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conflict of interest

The National Cancer Institute of Canada Clinical Trials Group is a peer-reviewed, independent cancer clinical trials cooperative group that in the conduct of its trials includes collaboration with multiple pharmaceutical companies.

references


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