Health Outcomes Research in Medicine

ORIGINAL RESEARCH ARTICLE

HEALTH ■ CLINICAL ■ POLICY

The Ends Justify the Mean: Outcome Measures for Estimating the Value of New Cancer Therapies

Andrew Davies, MSc[a], Andrew Briggs, DPhil[b], John Schneider, PhD[b], Adrian Levy, PhD[c], Omar Ebeid, MPH[b], Samuel Wagner, PhD[d], Srividya Kotapati, PharmD[d], Scott Ramsey, MD, PhD[e]

[a]Oxford Outcomes Ltd, Oxford, UK; [b]Oxford Outcomes Inc., Morristown, NJ; [c]Oxford Outcomes Inc., Toronto, ON, Canada; [d]Oncology Division, Bristol-Myers Squibb, New York, NY; and [e]Fred Hutchinson Cancer Research Center, Seattle, Wa

ABSTRACT

OBJECTIVE: Overall survival is a commonly reported end point in clinical trial publications and a key determinant of therapies' cost-effectiveness. Patients' survival times have skewed distributions. Outcomes are typically presented in clinical trials as the difference in median survival times; we compare median survival gain with the measure required for economic evaluation, the mean difference.

STUDY DESIGN: We summarize the relationships between median and mean survival in 4 parametric survival distributions and the relationship of the differences in these measures between trial arms and parameterized treatment effects. Parametric estimates of mean survival were compared with median survival in a case study of a recent trial in metastatic melanoma.

RESULTS: In a trial of alternative therapies in unresectable metastatic melanoma, median overall survival with ipilimumab alone was 10.1 months versus 6.4 months with gp100-alone (hazard ratio 0.66; $P = 0.003$). A log-normal parametric survivor function fitted the gp100 Kaplan-Meier function and a time ratio of 1.90 applied only after 90 days gave a suitable fit to the Kaplan-Meier function for ipilimumab, with mean survival difference of 7 months, compared with an estimate of 5.7 months employing a Weibull distribution, and with a 3.7-months median difference.

CONCLUSION: Parametric assessment of mean survival gain in clinical trials may indicate potential benefits to patients that observed medians may greatly underestimate.

KEYWORDS: Modeling; Oncology; Overall survival; Survival analysis

See funding, conflict of interest, and authorship disclosures at the end of this article.

The rapid increase in the cost of cancer therapeutics has renewed interest in methods for assessing the value of cancer treatments.[1-14] The impact of new oncology therapies is evaluated using a variety of end points, including tumor response, symptom alleviation, and time to treatment failure. In some instances, clinical symptom measures and biomarkers may play a role. Progression-free survival and overall survival are important end points.[15] The former has the advantage of being able to show significant effects with smaller sample sizes and shorter follow-up than is required for overall survival, while overall survival represents a direct and universally accepted measure of benefit and has the advantage of being easily and accurately measured.[15,16]

Both progression-free survival and overall survival benefits are commonly reported in clinical trial publications as the difference in median survival time between the 2 treatment arms. The use of median survival time is common because it is possible to estimate median survival before all patients have experienced an event, thereby allowing timelier reporting of estimates of survival gain as important oncology clinical trial results are disseminated.

Nevertheless, reimbursement authorities around the world are concerned with value for money of new oncology products and cost-effectiveness analysis is often employed to provide an estimate of value. In contrast to clinical evaluation, health economic evaluation is fundamentally interested in the mean costs and effects of treatment. This is because the remit of reimbursement authorities is to maximize total health gain for a population for a given budget. Only the mean cost and effect, when multiplied by the number of patients treated, gives the total cost and overall health gain for that patient group. The incremental cost-effectiveness ratio summarizes the additional value of treatments based on an estimate of the mean cost difference between 2 alternative treatments divided by the difference in their mean effects.[17]

In this article we explore commonly reported measures of survival in oncology trials with a view to understanding how these might differ from the preferred measure for economic evaluation — the mean survival time. We describe the relationship between the median and mean survival time for popular parametric survival distributions. Using data from oncology submissions to the UK's National Institute for Health and Clinical Excellence (NICE), we compare the ratios of reported median survival times with corresponding Cox proportional hazards ratios. Finally, we compare parametric estimates of mean survival with reported median survival in a case study of a recently published trial in metastatic melanoma to illustrate the practical importance of the issues.

MEASURES OF SURVIVAL IN CLINICAL AND ECONOMIC EVALUATION

Clinical trials in which the study end point is time to event (for example, disease progression or death) involve analysis of survival data typically characterized as containing censored and truncated survival times. Censoring includes administrative censoring due to a single study end date after patients enter the study at different times, and the loss of patients to follow-up over the course of the trial. Truncation relates to the maximum follow-up of survival times within a given study. Kaplan-Meier (KM) analysis addresses the issue of censoring and provides the product-limit estimate of the survivor function up to the maximum follow-up time, based on an assumption of independence between the censoring mechanism and the event of interest. Statistical tests such as the log-rank test[18] provide *P*-values for the overall difference between the KM survivor functions but do not provide a basis for estimation of mean survival difference which requires an estimate of the area under the complete survival curve. To obtain the area under the complete survival curve, it is also necessary to deal with the issue of truncation by projecting (extrapolating) beyond the maximum survival time in a study.

The probability of surviving beyond any time less than the final observation point can be read from the KM survivor function. In Figure 1, for example, the final observation point is at 5 years, at which time the proportions of patients surviving in the control and treatment arms are S_1 and S_2, respectively. Important