Non-inferiority Test on Survival Data

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Abstract

Frequently a non-inferiority trial is designed to confirm the absence of a meaningful difference between two active treatments. This meaningful difference is usually referred the non-inferiority margin. When the primary endpoint in the given trial is survival, procedure and interpretation may not be as simple as a case of the endpoint being proportion, e.g. response rate. A couple of methods for non-inferiority test are proposed for an application to survival data: (1) Non-inferior survival rates along the Kaplan-Meier curves and (2) Hypotheses based upon hazard rates are formulated.

Methods

(1) Non-inferior survival rates along the Kaplan-Meier (K-M) curves

Cumulative survival rates estimated by the K-M method can be compared at regular time intervals, e.g., every 3 months of the follow-up period until both groups have survival ≤ 25%. Two-tailed 95% confidence intervals around the difference in the K-M survival rates can be constructed. For the month(s) when the survival rate is greater than or equal to 90% for the better of the two treatment groups, a confidence interval that crosses zero and has a lower bound above –10% would be the criterion for non-inferiority (equivalence). For the months where the survival is between 80% and 89% for the better of the two treatment groups, a confidence interval that crosses zero and has a lower bound above –15% would be the criterion. For the months where the survival rate is 79% or less for the better of the two treatment groups, a confidence interval that crosses zero and has a lower bound above –20% would be the criterion. This method of data analysis for addressing non-inferiority is compatible with a guideline of the Division of Anti-infective Drug Products of the FDA[1], in which the equivalence margin is based on the proportions (response rates).

For the construction of the previously stated confidence intervals, non-parametric covariance adjustment could be applied for primary purposes to the life table counterparts of Kaplan-Meier estimates. Nonparametric covariance adjustment is expected to provide narrower confidence intervals via variance reduction in a manner that has no formal assumptions for an intention-to-treat analysis of a randomized trial[2]. The covariables for adjustment would include the stratification variables of randomization, if any, and the prognostic factors such as performance status, weight loss in previous six months, disease stage, brain metastases, age, gender, histological subtype, liver involvement and bone involvement in a cancer clinical trial

Since a 95% confidence interval for the difference in survival rates is repeated at the time intervals (e.g., every 3 months for the 36 months of the total follow-up period), the criterion for the

non-inferiority would be that the lower limit of the 95% confidence interval is greater than or equal to the specified bounds above, by the all, or all except one confidence intervals, in order to reduce possibly excessive Type II error relative to the multiplicity in 10 or more assessments at a "regular" time interval basis. Further simulation work is planned to assess the critical region regarding the multiplicity.

(2) The hypotheses based upon hazard rates are formulated as follows:

$H_0 : h_R(t) / h_T(t) \leq 0.75$ versus $H_1 : h_R(t) / h_T(t) > 0.75$, where $h_R(t)$ and $h_T(t)$ are hazard rates for the reference (active control) and experimental therapy, respectively.

Proportional hazards (Cox) regression modeling of prognostic factors can be employed to assess hazard rates: the model would include treatment, the stratification variables, and other prognostic parameters. This model for survival time can be the primary method to evaluate the hypotheses of non-inferiority for the comparison between the experimental therapy and the active control with adjustment for those prognostic factors prospectively stated in advance. A confidence interval at the 0.95 level for the treatment comparison in this Cox model then will be primary method to address the hypotheses for non-inferiority. The criterion for non-inferiority would be the lower limit of this confidence interval exceeding 0.75. The non-inferiority margin of 0.75 here is interpreted as a maximum survival estimate difference of about 10% between the two groups. The interpretation is based on the relationship between hazard function and the survivorship function, as estimated by the K-M curve, $h(t) = - d/dt [\log_e \{S(t)\}] = (-d/dt [S(t)]) / S(t)$. Conversely, $S(t) = \exp \{ - \int_0 h(x) dx \}$. Let $\theta = h_R(t) / h_T(t)$ denote the hazard ratio. Thus, $h_R(t) = \theta h_T(t)$ and so $S_R(t) = \{S_T(t)\}^{\theta}$. Also, $S_T(t) / S_R(t) = \{S_R(t)\}^{(1-\theta)/\theta}$.

Discussion

Both proposed methods will be discussed using an example of actual cancer clinical trial data. Further development of the methods will also discussed.

REFERENCE

Center for Drug Evaluation and Research, FDA, U.S. Dept. of Health and Human Services (1995). Guidance for Industry: Points to consider for anti-infective drug development

Tangen, K. and Koch, G. (1999). Non-parametric analysis of covariance for hypothesis testing with log-rank and Wilcoxon scores and survival rates estimated in a randomized clinical trial. J Biopharmaceutical Statistics 9(2), 307-338

RESUME

Des essais de non-infériorité sont couramment pratiqués dans le but de confirmer l'absence de différence d'efficacité cliniquement significative entre deux traitements actifs. Lorsque le critère principal est de type survie, les méthodes et l'interprétation ne sont pas aussi simples que dans le cas d'un critère binaire (tel que le taux de réponse, par exemple.) Deux méthodes adaptées aux essais de non-infériorité dans le cas de données de survie sont proposées, à savoir d'une part la comparaison des taux de survie le long des courbes de Kaplan-Meier, et, d'autre part, une approche basée sur les forces de mortalité. Un exemple réel dans le cas d'un essai en oncologie est présenté. Des développements possibles de ces méthodes sont également décrits.