Optimal multi-stage phase II design with sequential testing within each stage for evaluating survival probabilities

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Typically, in phase II cancer clinical trials the agent's activity is quantified by change in the tumour size. In recent years, new cytostatic agents delay disease progression without necessarily reducing the tumour size. This leads to increased interest in using time to event endpoints, such as overall survival or progression-free survival for phase II evaluation. Multi-stage phase II designs, allowing for early stopping of the study if interim results are disappointing, based on the simple proportion of patients surviving a specified time are not appropriate for monitoring survival probability, since information from censored patients with incomplete follow-up is ignored. The suggested multi-stage designs (Case and Morgan, 2003, Lin et al., 1996) for monitoring survival probabilities allow acceptance of the agent only at the last stage, similarly to the Simon's two stage designs for simple proportion hypotheses (Simon 1989). In these designs, the null hypothesis H_0: $S(x^*) \leq S_0(x^*)$ is tested versus the alternative hypothesis H_A: $S(x^*) > S_0(x^*)$, where x* denotes the survival time of interest and $S(\cdot)$ denotes the survival function.

We propose an alternative multi-stage design for evaluating survival probabilities at interim looks in which the study can be terminated when there is sufficient evidence for acceptance or for rejection of the agent of interest. We define the corresponding hypothesis H_0: $S(x^*) \leq S_0(x^*)$ versus H_A: $S(x^*) > S_A(x^*)$, where $S_0(x^*) < S_A(x^*)$. These hypotheses consist of two non-complementary events and can introduce ambiguity in the evaluation of type I and II errors and the choice of the appropriate practical decision at the end of the study. To address the issue of non-complementary events we propose a class of designs in which we test two hypotheses sequentially in each stage. In stage i, $i=1,\ldots,k$, we first test the hypothesis H_{01}: $S(x^*) \leq S_0(x^*)$ versus H_{A1}: $S(x^*) > S_0(x^*)$. If we reject H_{01}, we cannot consider that the therapy is ineffective, so we test the hypothesis H_{02}: $S(x^*) \geq S_A(x^*)$ versus H_{A2}: $S(x^*) < S_A(x^*)$, in order to examine if the therapy is effective enough to stop the trial. If H_{A2} is rejected then it is concluded that the agent warrants further study in a Phase III trial. If not, then the same testing procedure is repeated at stage i+1.

During the design stage, estimates of survival probabilities can be obtained by making the assumption that expected survival time follows an exponential distribution or variants. This is important since observed survival has been shown to deviate from simple exponential distribution, as in the case of the non-constant hazard rates of death according to ER negative and positive expression for breast cancer tumours (Anderson et al 2006). Under the above conditions and the assumption that the accrual rate is fixed, we develop designs that minimize the expected study length (ESL), while satisfying specific upper bounds for the α and β error levels.

References

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