Dose-escalation designs for combination & dose-schedule studies

MRC Biostatistics Unit

Practical 3: Dose-escalation in a trial with unknown ordering

You are asked to design a Phase I dose-escalation clinical trial of a combined induction chemotherapy and immunotherapy for patients with high-risk neuroblastoma. The clinical team would like to evaluate the following schedules

- 2 days immunotherapy AFTER chemotherapy (S_1)
- 3 days immunotherapy AFTER chemotherapy (S_2)
- 4 days immunotherapy OVERLAP with chemotherapy for 1 days (S_3)
- 4 days immunotherapy OVERLAP with chemotherapy for 2 days (S_4)

that will be administered as one of the following six treatment regimens: It is known that, R_1 and R_2

Regimen	R_1	R_2	R_3	R_4	R_5	R_6
Cycle 1		S_1	S_2	S_3	S_3	S_4
Cycle 2	S_1	S_2	S_2	S_3	S_4	S_4

are the least toxic regimens, and R_6 is the most toxic regimens. However, the clinicians do not know what is most or least toxic among R_3, R_4, R_5.

The escalation will be driven by the safety of the regimens only. The objective of the trial is to study safety and tolerability of the combination given under various schedules and to identify the maximum tolerated combination-schedule (MTC) associated with 30% risk of a DLT. The acceptable toxicity range is 25%-35%. The safety outcome of interest is a dose-limiting toxicity (DLT) within the two cycles of the treatment (6 weeks). Up to 30 patients are planned to be enrolled in the trial and no early stopping rules are currently imposed. If no DLTs are observed in the trial, the clinical team would like to escalate from R_1 to R_6 in the order the regimens are numbered. Given the uncertainty in the toxicity ordering for some of the combination, you asked to explore the two-stage POCRM design implemented in the `R`-package `pocrm` for the considered trial. Use `P3-template.R` as a starting point.

(a) Specify all possible orderings that can occur in this trial. Using skeleton

$$(0.10, 0.21, 0.24, 0.30, 0.35, 0.40)$$

and function `getwm()` construct ordering-specific working models (skeletons). Examine the output to check that working models correctly reflect the assumptions on the known (and unknown) ordering of toxicity.

(b) The clinical team believes that any of the specified ordering is equally likely. Specify the corresponding prior probability of each ordering `prior.o`

(c) You now need to evaluate the performance of the proposed form of the POCRM design under various scenarios of true toxicity orderings. As a starting point, use the scenarios from L6 (Slide 9). Run the simulation under the 3 scenarios. Compare the performance of the POCRM to the single-agent designs (reported in L6). Does it perform better or worse? Why? What metrics did you consider for the conclusion?

(d) A comprehensive simulation study could include scenarios covering all possible toxicity orderings. Do the scenarios above cover all the possibilities? If yes, explain why. If no, please add variants of the Scenario 1.1 covering the missing cases and conduct the simulations.

(e) After some discussions, the clinical team agreed that it is less likely that R_5 will be less toxic than R_3. Specifically, it is thought to be half as likely. Refine the POCRM design to reflect this change in the prior beliefs. Run the simulation for the refined POCRM. Do you need to reconsider the scenarios for the simulation study? Their interpretation? Does the POCRM perform better in one scenarios than in others? Why?

(f) Right after you complete the simulation study and write up of the result, you are invited to an online meeting at which you are notified that the clinical team decided to refine R_5 such that it is not clinically possible that R_5 will be less toxic than R_3. How will this change the POCRM design. Please make the appropriate changes. Would this change the scenarios under which you evaluate the design. How does this performance compare to the single-agent designs and to the first obtained results. Why?

(g) Fortunately, there were no further changes, and it is the time to conduct the analysis.

- Assume that the 0/3 DLTs were observed on R_1 and then 1/3 DLTs on R_2. Fit the POCRM using `pocrm.imp`. What is the probability of each ordering? How does it compare to the prior probability of orderings? What is the next recommended dose? Why? Would you suggest to follow this recommendation?
- Assume that given 1 DLT at R_2, the decision is to stay at R_2 where 0/3 DLTs is observed. What are the estimates now? How the probability of each orderings are updated? Why? What would be model's recommendation? Yours?
- Assume that the decision is to escalate to R_3 where 1/3 DLTs is observed. What are the estimates now? How the probability of each orderings are updated? Why? What would be model's recommendation? Yours?
- Since 1 DLT is observed, the clinical team decided to overrule the model and de-escalate to a less toxic dose. What would be your recommendation?

(h) Could you recommend the developed design for the use in the actual study? If yes, why? If not, what is missing?