

Application of multinomial (MN) phase II designs in trials of targeted agents.

R. Jamal, R. A. Goodwin, D. Tu, W. Walsh, E. A. Eisenhauer; NCIC Clinical Trials Group, Kingston, ON

Abstract Text:

Background: The commonly used Fleming (FL) and Gehan phase II designs make recommendations on activity or early termination based on response rate (RR). The MN design, by incorporating early progression (PD) and RR, has been shown to perform more efficiently than FL or Gehan as assessed by appropriate early stopping for inactivity in phase II trials of cytotoxic agents [Dent S, 2001]. Because RR is a controversial endpoint for targeted agent trials, we compared the performance of MN vs. FL designs in a series of NCIC CTG phase II trials.

Methods: We applied two MN stopping rules (MNA and MNB) to 15 trials evaluating single agent targeted therapies. All trials were conducted using a FL design (Ho: proportion responding $p_r \leq 5\%$ vs. Ha: $p_r \geq 20\%$). The hypotheses were: for MNA: Ho: $p_r \leq 5\%$ OR proportion with PD $p_p \geq 60\%$ vs. Ha: $p_r \geq 20\%$ and $p_p \leq 40\%$; for MNB: Ho: $p_r \leq 5\%$ AND $p_p \geq 60\%$ vs. Ha: $p_r \geq 20\%$ or $p_p \leq 40\%$. The trial would stop at stage 1 by MNA if either the response OR the PD criterion for stopping were met and by MNB only if both the response AND the PD criteria for stopping were met. Sequential patient data were reviewed in each trial to tabulate a stop/go decision at the end of stage 1 based on FL, MNA and MNB and also to determine if each agent was considered active by that design at end of study. **Results:** FL stopped 8/15 trials: of 7 trials completing stage 2, only 2 met FL criteria for activity. The MNA rule would have stopped 12/15 trials, including 2 that the same design would have accepted as active based on the final data. FL and MNA disagreed on early stopping in 4/15 trials, all of which were eventually rejected by FL. MNB did not recommend early stopping in any trial.

	No. Trials (n = 15)			
	Stopped end stage 1	Continued to stage 2	"Active" at end of study	Active at end of study and rejected stage 1
FL	8	7	2	N/A
MNA	12	3	5	2
MNB	0	15	at least 2*	0

*Stage 2 sample size for MNB design exceeded number pts actually enrolled in all cases so only rarely could activity be determined.

Conclusions: Using the PD hypotheses noted: MNA, which considered both RR and PD in assessing activity, stopped trials early more often than FL. MNB, which required only one of RR or PD to assess activity, never stopped a trial early. We plan to repeat this exercise using additional PD hypotheses to determine levels that would change MNB performance.