Size Matters

What Can We Learn from a Small Randomized Trial?

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I want to believe that continuation of 5-FU (5-Fluorouracil) with irinotecan (CPT-11) after 5-FU failure is of no use. It would be easier, probably safer, and more convenient. As discussed in the conclusions of the paper by Graeven et al. [1] in this issue of ONKOLOGIE, the FOCUS study [2] suggests otherwise; it suggests that there is some synergistic benefit from 5-FU, after it has failed, when it is combined with irinotecan. Given the limited preclinical synergy data for 5-FU plus irinotecan and the lack of preclinical synergy data in 5-FU-resistant tumors, the observation of the FOCUS trial is both surprising and hard to explain. This is in marked contradistinction to the situation with oxaliplatin, in which the synergism is robust, and both clinical and preclinical data support the continued need for 5-FU when oxaliplatin is given after 5-FU failure. Dr. Graeven and colleagues have presented a small study comparing irinotecan alone to irinotecan plus infusional fluorouracil following failure of first-line therapy. Their results tell me what I want to hear ... that the outcome with second-line CPT-11 is the same whether or not we continue 5-FU. Unfortunately, this study failed to accrue, and the originally targeted sample size of 215 was not achieved. As has been correctly noted by the authors, this greatly limits the interpretability of the results. A total of only 57 patients were randomized, and one cannot expect to be able to detect subtle differences between these two small groups. If we look, for example, at the primary end point of the study, progression-free survival, we see that although the 3.7 month medians are the same, the actual results may be as low as 2.7 or as high as 7.8 within the 95% confidence intervals. As such, all but the most dramatic of differences would not be discernible on this trial. Similarly, only the most substantial differences in response rate could be detectable with meaningful sensitivity, given the small sample size.

As has become popular when a phase III trial does not meet its accrual goals, the study has been published under the title of a 'randomized phase II'. It is noteworthy that in a randomized phase II trial, the appropriate primary endpoints are simply parallel phase II interpretations of the response, progression-

free survival, and toxicity data, rather than the statistical comparison of the two arms. The statistical hypothesis for such a comparison is really only appropriately tested in a full phase III study. A negative result, such as was seen, is expected from such a small comparison, and must be somewhat discounted on the basis of insufficient power to exclude a modest positive result. Had a positive result been seen, it would be the equivalent on an un-pre-planned, ad hoc analysis of a trial in progress, and would only carry weight if it exceeded the statistical criteria of an early stopping rule. A simple p value of less than 0.05 would be insufficient to establish significance under these circumstances. That is why, difficult and expensive though they may be, we must persevere in the conduct of large randomized trials if we are to answer questions regarding benefit.

In the conclusion of the discussion section, the authors state that the FOCUS trial (thus far presented only in abstract form) has demonstrated an overall survival advantage for the combination of 5-FU and irinotecan over irinotecan alone, and that this should dictate practice. This is a reasonable, albeit not universally accepted, interpretation of that complex and somewhat controversial trial. I would respectfully suggest, however, that this current study, given its small size and its attempt at phase III statistics in a randomized phase II setting, adds little to the discussion on this topic. The FOCUS trial does suggest a possible, although not well explained, role for the continuation of infusional 5-FU. As such, this question remains open, and clinicians must weigh the relative toxicities and inconvenience of continued infusional 5-FU against the potential for modest theoretical benefit.

References

- 1 Graeven U, Arnold D, Reinacher-Schick A, Heuer T, Nusch A, Porschen R, Schmigel W: A randomised phase II study of irinotecan in combination with 5-FU/FA compared with irinotecan alone as second-line treatment of patients with metastatic colorectal carcinoma. *Onkologie* 2007;30: DOI: 10.1159/000099636.
- 2 Seymour MT: Fluorouracil, oxaliplatin and CPT-11 (irinotecan), use and sequencing (MRC FOCUS): a 2,135-patient randomized trial in advanced colorectal cancer (ACRC). *J Clin Oncol* 2005;23(suppl):abstr 3518.