The CÁIRO and FOCUS Studies: Which Lesson Is to Be Learned?

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Disclosure: Miriam Koopman: None; Matthew T. Seymour: None; Cornelis J. A. Punt: None

In their update of recent clinical trials in metastatic colorectal cancer, O’Neil and Goldberg [1] discuss the results of the CApecitabine, IRinotecan, and Oxaliplatin in advanced colorectal cancer (CÁIRO) and Fluorouracil, Oxaliplatin, and CPT11—Use and Sequencing (FOCUS) studies. The CÁIRO study of the Dutch Colorectal Cancer Group prospectively compared the sequential with the combined use of chemotherapy when all three effective cytotoxic drugs in metastatic colorectal cancer, a fluoropyrimidine (capecitabine), irinotecan, and oxaliplatin, were made available to patients [2]. The results showed that upfront combination chemotherapy does not provide a statistically significant benefit in overall survival compared to sequential use of the same drugs, starting with capecitabine monotherapy. These results were confirmed by the FOCUS study of the Medical Research Council UK, in which the same question was addressed, albeit limited in most patients to the use of fluorouracil and either irinotecan or oxaliplatin, rather than all three drugs [3]. O’Neil and Goldberg state that although the CÁIRO and FOCUS studies appear to challenge the paradigm set by previous studies that demonstrated a survival advantage for upfront combination chemotherapy, two issues prevent a switch back to the use of upfront single-agent fluoropyrimidines for most patients: the small but nonsignificant benefit for combination therapy in these trials and the poor median overall survival durations for all treatment arms. We consider this statement an incorrect interpretation of our results.

First, the CÁIRO and FOCUS studies do not contradict previous study results, but are the first of their kind. Previous trials of first-line combination chemotherapy did not include effective salvage therapy as part of the prospective study design, and were therefore vulnerable to the effects of unplanned and unbalanced second- and third-line therapy. The importance of this aspect was most prominently shown in study N9741 by Goldberg et al. [4], which established oxaliplatin combined with continuous infusion 5-fluorouracil plus leucovorin (FOLFOX) instead of irinotecan and bolus 5-fluorouracil plus leucovorin (IFL) as the standard of care in first-line therapy in the U.S. In that trial, only 24% of patients received oxaliplatin after IFL failure, whereas 60% of patients received irinotecan after FOLFOX failure. Furthermore, only a small difference was observed in first-line progression-free survival (median, 1.8 months) but a much larger difference was observed in overall survival (median, 4.5 months). Taken together, these observations strongly suggest that the imbalance in effective salvage treatment may have been partly, or even largely, responsible for the apparent survival advantage with FOLFOX [5]. The CÁIRO and FOCUS studies were designed to clarify this issue. Second, the CÁIRO and
FOCUS studies were designed to demonstrate the superiority of upfront combination chemotherapy in terms of overall survival by predefined statistically significant margins, and both studies failed in this. We consider it inappropriate to draw conclusions from nonsignificant differences for which the studies were not designed. Third, we agree that some studies in first-line metastatic colorectal cancer have shown higher median overall survival times than CAIRO and FOCUS. However, apart from the pitfalls that may be involved in cross-study comparisons, this may be explained by the fact that CAIRO and FOCUS included a poor prognosis patient population. Good-prognosis patients with liver-only metastases that may become resectable after chemotherapy, although strongly represented in trials with longer median survival times, were excluded from FOCUS and were underrepresented in CAIRO.

So what lesson is to be learned from the CAIRO and FOCUS studies? Clearly the results of these studies do not argue against the use of upfront chemotherapy. In fact, because of its superior response rate, combination chemotherapy may still be preferred when downsizing of tumor is the primary goal, such as in patients with potentially resectable metastases or with severe cancer-related symptoms. However, in the remaining majority of patients with metastatic colorectal cancer, CAIRO and FOCUS have taught us that the sequential use of cytotoxics is a reasonable alternative to upfront combination therapy. We simply have more options for these patients, and that is progress as well.

REFERENCES