Modulation of 5-fluorouracil/leucovorin by trimetrexate—did it work?

In this issue of Annals of Oncology two independent randomized studies comparing weekly 5-fluorouracil (5-FU)/leucovorin (LV) with 5-FU/LV plus trimetrexate are reported [1, 2]. In addition, an integrated analysis of both studies to look at survival differences is presented [3]. The rationale for undertaking these randomized studies was strong: the addition of trimetrexate but not methotrexate to the 5-FU/LV combination was synergistic in the laboratory [4], and phase I and phase II studies were encouraging [5–7].

The need to do an integrated analysis of the two randomized studies was prompted by the Food and Drug Administraion (FDA) in the USA, when they changed criteria from progression free survival (PFS) to overall survival as the primary outcome measure for this trial. As neither study was adequately powered for this purpose, the integrated analysis was performed in order to detect survival differences at a statistical level. Problems with this analysis are: (i) that the dose of 5-FU used in the control arm differed in the two studies; (ii) as the US study was placebo controlled, additional LV was given to patients in the control arm; (iii) grade 3 or 4 diarrhea was less common in the European study, probably owing to the more aggressive use of loperamide; and (iv) criteria for declaring tumor progression differed in the two studies, and post protocol treatments (i.e. irinotecan) appeared to have differed between the two trials.

Therefore, the issues worth discussing are: (i) was survival the best outcome measure; (ii) was a placebo-controlled trial justified for the US study; (iii) is it appropriate to compare the two studies because of the differences noted above; and (iv) how do these results compare with survival data reported for combinations of 5-FU with irinotecan or oxaliplatin?

Based on discussions with the FDA, these studies were initially designed to detect a statistically significant difference in median time to progression of 80%, requiring a sample size of 300 patients. Neither study was adequately powered to detect survival differences at a statistically significant level. Survival as an endpoint has many problems, primarily that patients off study are not managed comparably from one institution to another, and access to new treatments differs from one country and institution to another. PFS is a meaningful endpoint, and allows comparisons requiring fewer patients. Several promising new drugs have not been approved by the FDA in the USA because of the need to demonstrate a survival advantage in every randomized trial over the control arm [e.g. raltitrexed (Tomudex), liposomal doxorubicin].

Was a placebo-controlled trial recommended by the FDA for the US trial justifiable? Placebo-controlled trials have their advantage in every randomized trial over the control arm [e.g. raltitrexed (Tomudex), liposomal doxorubicin].

The use of different doses of 5-FU in the control arms of the two studies is also worth commenting on. One would have expected that the PFS difference would be less in the European study than in the American study, as a result of the higher dose of 5-FU used in the control arm in the European study; in fact the PFS was significantly better ($P = 0.03$) in the experimental arm. Was this due to the early use of loperamide and less diarrhea in this trial, or the different criteria for progression (single lesion versus the sum of lesions), or both?

It is of interest to compare the PFS and survival data for patients on this study with recent randomized studies of 5-FU, and 5-FU with irinotecan or oxaliplatin. Irinotecan with 5-FU/LV produced a modest increase in survival over 5-FU/LV (14.8 months versus 12.6 months [8, 9]), not dissimilar to the integrated analysis data for the trimetrexate trial (13 months versus 14.6 months). Survival in the oxaliplatin plus 5-FU/LV versus 5-FU/LV arm in two randomized studies were comparable, i.e. thus far no survival advantage; however, in these studies the 5-FU/LV schedules differed from the weekly schedules in the trimetrexate trials and in the irinotecan plus 5-FU trial [10, 11].

Finally, where do we go from here? No one can deny that treatment of advanced colorectal carcinoma is unsatisfactory, and even if trimetrexate added to 5-FU/LV did improve the PFS by 5 weeks, is it worth it for the patient? The lack of significant hematological toxicity of this combination should prompt studies that add another agent to this combination. Another approach would be to determine whether molecular markers (thymidylate synthase, dihydropyrimidine dehydro-
genase) might be useful in selecting patients with a high probability of response. And, of course, we await the development of even more effective drugs for the treatment of this disease.

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References