Mature Results of Adjuvant Colon Cancer Trials From the Fluorouracil-Only Era

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In this issue of the Journal, Labianca et al. (1) report the results of a randomized trial comparing intraportal chemotherapy, systemic chemotherapy, or the combination of both regimens as adjuvant therapy for patients with Dukes’ stage B or C colon carcinoma. 5-Fluorouracil at a dosage of 500 mg/m² of body surface area with 5000 IU of heparin was given through the portal vein for 7 days, starting on the day of surgery (IP regimen). Systemic therapy involved intravenous administration of leucovorin at 100 mg/m² over a 2-hour period followed by bolus 5-fluorouracil at 370 mg/m² daily on days 1–5, repeated every 28 days for six cycles (SY regimen). Over 6 years, 1199 patients were randomly assigned to treatment during surgery, and 1084 patients deemed eligible were analyzed. A higher percentage of patients in the systemic therapy arm appeared to have a performance status of 1–2 and Dukes’ stage C colon cancer than in the other two arms (Table 1). Intraportal therapy was not started in 7%–10% of patients, whereas systemic chemotherapy was not started in 13%–15% of patients. No statistically significant difference was noted in 5-year survival among the treatment arms.

The rationale for administration of 5-fluorouracil by portal venous infusion is that, although most large metastases obtain their blood supply predominantly from the arterial circulation, the portal circulation may be important for micrometastases. The potential benefit of portal perfusion as adjuvant therapy has been tested in patients with colon and rectal cancer. In 1997, the Liver Infusion Meta-analysis Group reported on 3499 patients enrolled in 10 studies that evaluated portal venous infusion of cytotoxic drugs for 5–7 days in the immediate postoperative period (5-fluorouracil–heparin in eight trials and 5-fluorouracil–heparin plus mitomycin C in two trials) versus no additional therapy (2). When all patients were included (intention to treat), 42.1% of patients allocated to portal venous infusion had died compared with 47% in the control group, representing a 13.6% reduction in the annual odds of death ($P = .006$). Data on ineligible patients could not be provided for three trials, which introduces potential bias. Analysis restricted to the seven trials for which complete data were available revealed a mortality reduction of 10% ($P = .07$). The 5-year survival curve for all patients randomly assigned to treatment groups showed that the curves overlapped for the first 2 years and diverged thereafter. Since most recurrences occur within 2 years of initial surgery, one would expect the curves to separate during this period if there were a beneficial treatment effect. This result raises the possibility that the late divergence of the curves may be due to chance. Finally, there was no consistent association of portal vein infusion therapy on decreased risk of developing liver metastases among the trials.

The AXIS collaborators recently reported the results of a trial of adjuvant radiotherapy and 5-fluorouracil administered by portal venous infusion in patients with colorectal cancer (3). Over an 8-year period, 3583 patients were randomly assigned to surgery with or without 5-fluorouracil (1 g plus 5000 IU of heparin) daily for 7 days. Patients with rectal cancer could be randomly assigned to radiation therapy or to no radiation either...
before or after surgery. Portal venous infusion was not associated with a substantial improvement in survival either in the intention-to-treat analysis of all patients randomly assigned to treatment (hazard ratio [HR] = 1.0) or in an analysis restricted to those patients who underwent complete tumor resection (HR = .94).

Although insertion of a portal vein catheter is relatively simple and adds only 10–15 minutes to the operation, 10%–15% of patients randomly assigned to portal venous infusion never receive it. Why not use a peripheral vein? An intergroup study randomly assigned 800 patients with stage II or III colon cancer to six monthly cycles of bolus 5-fluorouracil–leucovorin with or without intravenous 5-fluorouracil for 7 days after surgery; the results have not yet been published.

What are my conclusions? Although the trial conducted by Labianca et al. was not sufficiently powered to prove equivalence of a 7-day course of portal venous infusion of 5-fluorouracil with 6 months of systemic bolus 5-fluorouracil–leucovorin, portal venous infusion of 5-fluorouracil did not appear to add to the benefit of treatment with 5-fluorouracil and leucovorin. Treatment with bolus 5-fluorouracil and leucovorin given either daily for 5 days every 4 weeks, or weekly for 6 of 8 weeks, for a duration of 6–8 months has established benefit in the treatment of lymph node–positive colon carcinoma (4–9). Although National Surgical Adjuvant Breast and Bowel Project (NSABP) C-04 and Intergroup 0089 trials used six 4-week and four 8-week cycles of the weekly schedule, respectively (7,8), more recent NSABP trials used three 8-week cycles. More recent trials indicate that the addition of oxaliplatin to leucovorin and bolus followed by infusional 5-fluorouracil was associated with a statistically significant improvement in disease-free survival at 3 years (78.2% vs. 72.9%; P = .002) in patients with stage II and III colon cancer (9). Efficacy data are pending from completed adjuvant colon cancer trials that compared bolus 5-fluorouracil and leucovorin with or without irinotecan or oxaliplatin and bolus followed by infusional 5-fluorouracil and leucovorin with or without irinotecan. An adjuvant trial comparing capecitabine with bolus 5-fluorouracil and leucovorin indicates an improved safety profile for capecitabine; efficacy data are pending (10). New agents, including bevacizumab (which targets vascular endothelial growth factor) and cetuximab (which targets endothelial growth factor receptor–positive colorectal cancer), are now therapeutic options in combination with 5-fluorouracil–based regimens.

With so many treatment options, how can we prioritize the adjuvant regimens to be tested? As the therapeutic efficacy of adjuvant regimens improves, the expected outcome after adjuvant therapy also improves. This improving outcome and the availability of active salvage regimens raise a number of issues. With a rapidly changing therapeutic landscape, the paradigm must shift to large randomized trials that enroll many thousands of patients and that are sufficiently powered to detect meaningful and realistic differences in outcome. Accrual must be completed over a few years; otherwise, the hypotheses being tested may be rendered irrelevant by emerging data from the advanced disease setting. Trials that use a simple design and are sufficiently powered to determine the superiority of one arm over another are most likely to yield definitive answers. From a registration perspective, clinical trials that clearly define the contribution of an individual agent are preferable, e.g., a test of treatment A plus treatment B versus treatment A alone. Equivalency trials require far more patients than do trials designed to establish superiority and therefore are not the wisest use of our limited clinical trial resources, particularly in the adjuvant setting. A change in the primary statistical end point to disease-free survival at 3 years rather than overall survival time at 5 years would allow for more timely trial completion and reporting. Careful discussions with the appropriate drug-regulatory agencies are crucial in the design of such studies if registration for this indication is contemplated. Consensus should be reached on whether the statistical goals for adjuvant protocols encompass the entire patient population (stage II and III) or have separate end points for each stage. Because the prognosis is better for stage II patients, many more patients than are typically enrolled in clinical trials would be needed to establish statistical significance of any potential disease-free or overall survival advantage. Unless the number of cancer patients participating in clinical trials dramatically increases, it may be unrealistic to prospectively plan to analyze stage II and III patients separately. Because there is currently no international consensus as to whether adjuvant trials should be conducted separately for colon and rectal cancer, or whether both primary sites should be included, cross-trial comparisons are problematic. The clinical research strategy for the adjuvant therapy of colon cancer must be focused, yet flexible, to accommodate the evolving status of available novel therapies.

REFERENCES


