The Role of Irinotecan and Oxaliplatin in the Treatment of Advanced Colorectal Cancer

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The article by Drs. Khayat and Gil-Delgado outlines the exciting new developments in the treatment of advanced colorectal cancer with irinotecan (CPT-11 [Camptosar]) and oxaliplatin. Although the development of these drugs provides an alternative to fluorouracil (5-FU) in the treatment of this common tumor, it is still unclear how to optimally integrate these promising compounds into therapy for colorectal cancer.

Improving the Efficacy of 5-FU

Fluorouracil has remained the mainstay of the treatment of advanced colorectal cancer for over 40 years. Unfortunately, only about 20% of patients who receive 5-FU demonstrate objective responses by standard criteria. Over the past 25 years, a tremendous effort has been made to improve the efficacy of 5-FU. One such line of research has shown that, compared with bolus administration, protracted intravenous infusion produces a marginally higher rate of response but is also associated with reduced toxicity.[1,2]

Biochemical modulators—eg, methotrexate, interferon-alpha, and, most extensively, leucovorin—have also been explored to increase the antitumor activity of 5-FU. In a meta-analysis of nine randomized trials of 5-FU alone vs 5-FU plus leucovorin for advanced cancer, a significant improvement in response rate was seen in patients who received 5-FU and leucovorin.[3] However, this level of improvement in response rate failed to translate into a significant survival advantage.

Irinotecan’s Role

In 1996, based on trials reviewed by the US Food and Drug Administration (FDA),[4] irinotecan was approved as a second-line treatment for patients with colorectal cancer whose disease had progressed after 5-FU-based therapy. Initial approval was based on tumor response alone. The survival benefit of irinotecan as a second-line treatment in colorectal cancer refractory to bolus 5-FU was clearly shown in two phase III randomized studies conducted in Europe. The results of those studies led to full approval of this drug in the United States.[5,6]

The survival benefit of irinotecan administered in combination with 5-FU and leucovorin as first-line treatment for advanced colorectal cancer was demonstrated recently in two phase III randomized studies. The first trial compared weekly irinotecan plus 5-FU/leucovorin to 5-FU/leucovorin (Mayo regimen) or weekly irinotecan.[7] Objective response rates documented by investigators were noted in 50% of patients receiving the three-drug combination vs 28% of patients receiving 5-FU/leucovorin (confirmed response rate: 39% vs 21%, P < .001). Median survival for the irinotecan/5-FU/leucovorin arm was 14.8 months vs 12.6 months for the 5-FU/leucovorin arm (P = .04). Grade 3 (severe) diarrhea was more common during treatment with irinotecan/5-FU/leucovorin, but the incidence of grade 4 (life-threatening) diarrhea was similar in both groups.

The other trial, conducted in Europe, also found a significant advantage in favor of the irinotecan/5-FU/leucovorin combination vs infusional 5-FU/leucovorin in terms of median overall survival (17.4 vs 14.1 months, P = .035), progression-free survival (6.7 vs 4.4 months, P < .001), and...
confirmed objective response (35% vs 22%, \( P < .005 \)).[8] All these end points demonstrated the modest but definite superiority of the combination of irinotecan, 5-FU, and leucovorin.

Unresolved Issues

After many years of clinical trials in colorectal cancer, however, several issues remain unresolved. Data from the European trials suggest that infusional 5-FU in combination therapy might be a better approach, both in terms of activity and toxicity. Whether sequential rather than concomitant administration of these drugs could achieve a similar effect with less toxicity is still somewhat uncertain. Retrospective data from the combination trials suggest that a survival benefit is maintained, even when the majority of patients assigned to single-agent therapy initially received subsequent second-line chemotherapy or other salvage treatments. Only a well-designed trial with a fixed crossover design, such as the MRC CR-08 ("FOCUS") trial in the United Kingdom, may find a definitive answer.

Furthermore, should the combination of irinotecan, 5-FU, and leucovorin be considered as the first-line treatment in a subgroup of patients with poor performance status (\( \geq \) ECOG 2), or with abnormal organ system function for survival, toxicity, and clinical benefit? Ultimately, biological markers that may predict response or toxicity from standard chemotherapy drugs may help determine which patients should receive irinotecan, 5-FU, and leucovorin as the first-line treatment.

Adjuvant Chemotherapy

Historical controls, from the era prior to standard adjuvant chemotherapy, demonstrated cure rates for stage III (lymph node positive) colon cancer of about 40% to 50%.[9] Adjuvant chemotherapy with 5-FU/leucovorin increased the 5-year overall survival rate to 60% or 65%.[10,11] Since the degree of antitumor activity may improve the success of adjuvant treatment, regimens with higher antitumor response rates could logically be expected to provide superior results in the adjuvant setting. An ongoing phase III US intergroup study (Cancer and Leukemia Group B [CALGB]-89803) that is randomizing patients with stage III colon cancer to either standard weekly 5-FU/leucovorin or irinotecan, 5-FU, and leucovorin may provide the answer.

There are also several similar trials (eg, ACCORD2, AERO R98) in Europe evaluating the same issue, with the use of infusional 5-FU methods. Because all patients with metastatic disease may not benefit equally from combination chemotherapy, all patients at different risks in the adjuvant setting may not necessarily require or achieve the same degree of benefit from more intensive treatment approaches. Trials specifically addressing high-risk node-positive patients may provide early and more profound evidence of the benefit achieved with combination chemotherapy.

Role of Oxaliplatin

Oxaliplatin, a diaminocyclohexane (DACH) platin, inhibits DNA replication and transcription through the formation of intra- and interstrand DNA adducts. The drug has demonstrated synergistic antitumor activity in combination with 5-FU and leucovorin both in vitro and in vivo.[12,13] In phase II trials, the clinical activity of oxaliplatin as first-line monotherapy has been shown to be similar to that of single-agent irinotecan.[14] Phase II trials evaluating the combination of oxaliplatin and 5-FU/leucovorin as initial therapy for patients with metastatic colorectal cancer (using chronomodulated drug administration schedules) suggested increased cytotoxicity, manifested by encouraging response rates, as well as improved progression-free and overall survival.[15,16]

Based on these encouraging data, European investigators conducted two randomized trials comparing oxaliplatin in combination with 5-FU and leucovorin vs 5-FU/leucovorin alone as first-line therapy in patients with metastatic colorectal cancer (EFC 2961 and EFC 2962).[17,18] The results of these trials showed a statistically significant benefit in objective response rate favoring oxaliplatin (53% vs 16% in EFC 2961; 50.7% vs 22.3% in EFC 2962), and progression-free survival (8.7 vs 6.1 months, \( P = .048 \), in EFC 2961; 9.0 vs 6.2 months, \( P = .0003 \), in EFC 2962). Although a trend toward a longer median survival was seen in the oxaliplatin-treated groups, the difference did not achieve statistical significance in either study (16.2 vs 14.7 months, \( P = .12 \), in EFC 2962; 19.4 vs 19.9 months in EFC 2961). Because oxaliplatin did not demonstrate a detectable impact on prolonging
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Overall survival, it was not approved by the FDA for use in the first-line treatment of advanced colorectal cancer.

Conflicting Results?

The explanation for this discrepancy is not clear. Subtle, but clinically important differences in baseline patient characteristics could have obscured assessment of the impact of oxaliplatin on survival. When these baseline differences were taken into account by Cox regression analysis, overall survival was significantly enhanced by the addition of oxaliplatin to first-line therapy in the EFC 2962 study ($p = .0001$).[17]

Other possible explanations are that the effects of oxaliplatin are too transient to have an impact on overall survival, or that the use of other salvage therapies (eg, surgery or irinotecan) influenced survival results. It is also possible that the infusional 5-FU/leucovorin control arm in both trials was more active than the bolus control arms in other studies, manifested by an unusually good survival among patients in the control arms in both oxaliplatin trials.

Of patients in the control arm, 57% received oxaliplatin after treatment with 5-FU/leucovorin failed in EFC 2961, and 37% of patients in EFC 2962 received poststudy chemotherapy with oxaliplatin and/or irinotecan as well as salvage surgery. The sample size of both studies was relatively small, which may explain why significant differences in response rate and progression-free survival did not translate into a statistically significant survival benefit. This underscores the need for trials with adequate sample sizes that are able to properly assess modest yet clinically worthwhile benefits.

Further Studies

Studies of the combination of oxaliplatin and 5-FU/leucovorin in the second-line setting have shown encouraging results.[19] However, several important questions still need to be answered, including the impact of re-treatment with alternative methodologies of 5-FU/leucovorin in the combination. As a second-line therapy, how much activity is due to oxaliplatin, and how much is secondary to a change in the dose or schedule of 5-FU/leucovorin?

A pivotal trial currently underway in the United States is attempting to answer these questions. Patients with advanced colorectal cancer in whom disease progressed after treatment with irinotecan/5-FU/leucovorin are being randomized to one of three arms: (1) a control arm of bolus plus infusional 5-FU and leucovorin (de Gramont regimen), (2) oxaliplatin as a single agent every 2 weeks, or (3) the combination of 5-FU, leucovorin, and oxaliplatin.

Summary

In summary, the combination of irinotecan, 5-FU, and leucovorin has been confirmed as a new first-line treatment for advanced colorectal cancer. Several important clinical trials are in the process of clarifying the role of oxaliplatin in the treatment of patients with metastatic colorectal cancer.

In addition to developing new agents for this disease, clinical research should be directed at optimizing and individualizing therapy for patients to achieve maximal clinical benefit. In this regard, the use of combination chemotherapy before planned hepatic resection for liver metastases is among the most exciting possibilities for improvement, and may convert the therapy of some patients from palliative to curative treatment.

References:


