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Oxaliplatin: Is It a New Standard Weapon for Colorectal Cancer?

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INTRODUCTION

In this issue of Cancer Research and Treatment, Kwon H-C et al. reported the results of oxaliplatin, infusional fluorouracil (FU) and leucovorin (LV) as first-line therapies for metastatic colorectal cancer. In this study, 55 patients were treated with oxaliplatin 85 mg/m^2 each as a 2-hour infusion at day 1 and LV 20mg/m^2 over 10 minutes. This was followed by a 400 mg/m^2 bolus and a 22-hour continuous infusion of 600 mg/m^2 FU at day 1~2, repeated every 2 weeks. The objective response was 40%; the median time to progression was 6.6 months (95% CI: 4.98~8.02 months); and the overall survival was 17 months (95% CI: 9.15~24.85 months). Major toxicities were neutropenia, thrombocytopenia, nausea/vomiting, diarrhea, neuropathy, which ranged from grade 1 to 2 in terms of severity (1). The treatment schedule was same as FOLFOX4 protocol with the exception of the leucovorin dose.

Fluorouracil has been the standard treatment for advanced colorectal cancer. The response rate of fluorouracil for metastatic colorectal cancer is approximately 20%. There are various ways to administer fluorouracil, and a "loading" regimen (consisting of an intravenous bolus of the drug for five consecutive days every four to five weeks) and a weekly regimen (consisting of one intravenous bolus every week) are the two most commonly used methods in the United States. In Europe, on the other hand, the schedule of prolonged intravenous infusion is popular. Several controlled trials and a meta-analysis suggest that the prolonged-infusion approach results in a marginally higher rate of response, but only a negligible difference in survival (2). Another pharmacologic strategy that is used to increase the efficacy of fluorouracil is the use of reduced folate leucovorin. A meta-analysis of nine randomized trials in which the combination of fluorouracil and leucovorin was compared with fluorouracil alone in patients with advanced colorectal cancer who had received no prior therapy revealed that the combination significantly increased the probability of the tumor response but only minimally increased the survival (3).

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Recently, new drugs for advanced colorectal cancer have been introduced, including oxaliplatin, irinotecan, and capecitabine. Oxaliplatin, a third-generation platinum compound with a 1, 2 diaminocyclohexane carrier ligand, is active against human colon-cancer cell lines and synergistic with fluorouracil *in vitro* (4). It has a different spectrum of activity compared to cisplatin. Single-agent oxaliplatin showed objective response rates between 10% and 11% in previously treated patients (5). Phase III trial that compared an oxaliplatin/FU/LV (FOLFOX4 protocol) with standard infusional FU/LV (LV5FU2 protocol) as the first-line treatment in advanced colorectal cancer was reported by de Gramont et al. (6). The oxaliplatin-based protocol showed a substantial increase in activity, with significant effects on the response rate (50.7% vs 22.3%; p=0.0001) and the progression-free survival (9.0 vs 6.2 months; $p < 0.0001$). However, this increased efficacy did not translate into a significant prolongation of overall survival (16.2 vs 14.7 months). Neutropenia, diarrhea, nausea/vomiting, and mucositis were significantly more likely to occur in the oxaliplatin group with moderate severity, exception of neutropenia.

The results of Kwon's trial were similar to the de Gramont et al. trial in terms of survival and toxicities, although the response rate was minimally lower in Kwon's trial. The difference of these two trials was that de Gramont et al. used a high dose, while Kwon used a low dose. In comparing high and low doses of leucovorin in the adjuvant therapy for colorectal cancer in the INT0089 trial, there was no difference, and the high dose arm had a greater incidence of diarrhea (7). Ducreaux M et al. (8). compared LV5FU2 and low dose leucovorin LV5FU2 in metastatic colorectal cancer. There were no survival differences. Thus, the dosage of leucovorin for colorectal cancer has little effect on the variability of responses. The low dose leucovorin FOLFOX4 schedule is less expensive yet has the equivalent effect of the classic FOLFOX4.

Irinotecan, a semi-synthetic derivative of camptothecin, inhibits topoisomerase I. In previously treated patients, the objective response to irinotecan is approximately 15%, and the major toxicity is troublesome diarrhea. Saltz LB et al. reported irinotecan plus fluorouracil and leucovorin (IFL) comparing FU/LV or irinotecan alone for metastatic colorectal cancer. In this trial, patients who were treated with IFL had a higher probability of an objective response (39% *vs.* 21% and 18%, respectively), a longer time to progression (7 months vs. 4 months and 4 months), and a longer median survival (15 months vs. 13 months and 12 months). Diarrhea and neutropenia were the

most prominent side effects (9). Douillard JY et al. compared infusional FU/LV (de Gramond protocol) with irinotecan plus FU/LV infusion (FOLFIRI) in a randomized phase III trial. The irinotecan combination demonstrated a significantly higher efficacy by demonstrating a longer survival time (overall survival 17.4 *vs.* 14.1 months, p=0.031) (10).

Goldberg et al. reported a large randomized trial, in which trial patients were randomly assigned to receive irinotecan and bolus fluorouracil plus leucovorin (IFL), oxaliplatin and infused fluorouracil plus leucovorin (FOLFOX), or irinotecan and oxaliplatin (IROX). The FOLFOX regimen is more active in terms of the response rate and time to progression, more efficacious in overall survival, and less toxic than the IFL regimen. The IROX regimen is better than IFL as well, but only in terms of overall survival because its toxicity is worse with regard to vomiting and paresthesias(11). This finding supports the conclusion that the FOLFOX may be a first-line standard treatment for advanced colorectal cancer.

The summary of the advancements in the first-line treatment of metastatic colorectal cancer through randomized trials during the last 20 years is as follows. FU was superior to the best supportive care, and FU/LV was in turn superior to FU, though with more toxicity. IFL was subsequently more efficacious than FU/LV at the cost of additional toxicity. FOLFOX is more efficacious than both IFL and IROX without the additional toxicity. IROX regimen is as efficacious as IFL, but is more toxic. In conclusion, oxaliplatin or irinotecan combined with FU/LV is more efficacious than FU/LV, and infusional FU/LV is less toxic than bolus FU/LV, and oxaliplatin, irinotecan, and FU/LV triple combination, which is unlikely used due to severe toxicity. Finally, the infusional FU/LV is the best partner for a combination with oxaliplatin or irinotecan. It will be necessary to compare FOLFOX vs FOLFIRI in order to further confirm that FOLFOX is the first-line standard treatment for advanced colorectal cancer. Another unresolved problem is that the prolonged infusion is inconvenient, cumbersome, and more expensive. Because oral fluoropyrimidines are as effective as infusional FU, oral fluoropyrimidines, such as UFT, capecitabine (Xeloda) and TS-1, can be substituted with infusional FU. Further more, we can choose the combined use of chemotherapy and a targeted agent, such as cetuximab and bevacizumab. Phase III trials of these agents are ongoing now.

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