Oncology Issues

ISSN: 1046-3356 (Print) 2573-1777 (Online) Journal homepage: https://www.tandfonline.com/loi/uacc20

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To cite this article: Lilian Delmonte (1997) More News about Oxaliplatin, Oncology Issues, 12:6, 28-28, DOI: 10.1080/10463356.1997.11904722

To link to this article: https://doi.org/10.1080/10463356.1997.11904722

Published online: 18 Oct 2017.

More News About Oxaliplatin

As reported in the last *Oncology Issues*, Oxaliplatin, a novel type of platinum drug, has been shown to have activity against human ovarian cancer. French phase II-III trial data also suggest potential clinical benefit from incorporating oxaliplatin into the therapeutic regimen for treating advanced colorectal cancer. Colorectal cancer responds poorly to conventional chemotherapeutic agents other than 5-FU. Even with 5-FU, the standard agent for treating metastatic disease, only 25 to 30 percent of patients achieve long-term response.

Oxaliplatin is similar to 5-FU in that it kills cancer cells by promoting interstrand DNA cross-linking, but differs in that its antitumor action also involves a mismatched DNA repair mechanism and has little overlapping toxicity. Its only dose-limiting toxicity is a cumulative but reversible peripheral sensory neuropathy that is generally manageable by dose reduction or suspension.

First-line monotherapy. In an interview with *Oncology Issues*, Yves Bcouarn, M.D., a medical oncologist at the Institut Bergonie of the Comprehensive Cancer Center in Bordeaux, France, said that preliminary results of a multicentric phase II trial were confirming earlier reports that oxaliplatin (130 mg/m^2/day, infused IV q 21 d) is active as a single agent in previously untreated metastatic colorectal cancer. Twenty-seven percent of thirty-eight patients achieved PR lasting approximately four months. Patients who progressed on oxaliplatin usually had 5-FU with leucovorin rescue (5-FU/LV) added to their treatment regimens. Median one-year survival was 53 percent.

First-line combination therapy. In a subsequent randomized phase III trial performed under the auspices of the International Organization for Cancer Chronotherapy, the efficacy of combining oxaliplatin with 5-FU/LV was evaluated at fifteen European centers in 200 patients with previously untreated metastatic colorectal cancer. Sylvie Giachetti, M.D., assistant director of the Chronotherapy Center at the Hôpital Paul Brousse in Villejuif, told the ASCO audience that patients were randomized to receive multiple course of 5-FU (700mg/m^2/d x 5d) plus leucovorin (300 mg/m^2/d x 5d) by chronomodulated infusion (peak delivery at 4 a.m.), with or without oxaliplatin (125 mg/m^2, d 1) given by six-hour flat IV infusion. She explained that giving 5-FU/LV by chronomodulated rather than flat infusion increases the antitumor efficacy of 5-FU on a mg/mg basis. Response was

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evaluated at nine-week intervals by X-ray and computerized tomography (CT) scans. Results were read at the individual centers and confirmed in a blinded fashion by a panel of independent radiologists.

Giachetti told *Oncology Issues* that patients in the combination therapy arm achieved a significantly higher rate of objective response than those in the 5-FU/LV monotherapy arm (34 percent vs. 12 percent), and manifested a strong but statistically nonsignificant trend toward increased progression-free survival (7.9 vs. 4.3 months). An unexpected finding was that median overall survival, comparable for the two study arms (19.4 vs. 17.6 months) was longer than the eleven- to thirteen-month survival usually achieved with 5-FU/LV-based regimens in this setting.

Giachetti indicated that evaluation of the survival data was complicated by the fact that the study protocol allowed patients whose metastases had become resectable—twenty-one in the 5-FU/LV arm and twenty-seven in the 5-FU/LV plus oxaliplatin arm—to have responding metastases removed surgically. In addition, patients who failed on 5-FU/LV only were allowed to receive oxaliplatin-based therapy, and those who failed 5-FU/LV plus oxaliplatin were allowed to go on to alternate therapies including a more intensive 5-FU/LV regimen and novel agents such as trinotecan.

Overall, Giachetti pointed out, the addition of oxaliplatin did not appear to exacerbate the toxicity profile of 5-FU/LV, but did induce reversible peripheral sensory neuropathy in 13 percent of patients. Thus, the addition of oxaliplatin significantly improves the efficacy of chronomodulated 5-FU/LV as first-line therapy for metastatic colorectal cancer with acceptable toxicity.

Salvage therapy. In an ongoing multicenter phase II European study coordinated by Thierry Andre M.D., an oncologist in the section of medical oncology at Hôpital Tenon in Paris, ninety-nine patients with metastatic colorectal cancer who had progressed on high-dose 5-FU (400-500 mg/m^2/day, infused IV, x1-2d q 2 wk) had oxaliplatin (85 mg/m^2, IV, x1d q 2 wk) added to their treatment protocol. At one-year interim analysis, Andre told *Oncology Issues* at an ASCO poster interview, 27 percent of seventy-one evaluable patients had achieved PR. Consistent with the data of others, he found cumulative peripheral neuropathy to be the only dose-limiting toxicity of oxaliplatin.

Andre concluded, "These preliminary results confirm previous reports of clinical synergy between oxaliplatin and 5-FU in 5-FU-resistant metastatic colorectal cancer."

—Lilian Delmonte, D.Sc.