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ASCO Meeting Update

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ASCO Meeting Update

CONTROLLING NAUSEA: ORAL DRUGS VERSUS INFUSIONS

Freeing chemotherapy patients from intravenous lines offers a great measure of convenience. An impediment has been the understanding that IV formulations of antiemetic agents are more effective than oral ones for controlling nausea and vomiting associated with chemotherapy. Data from two large-scale randomized, double-blinded, multicenter trials presented at the 33rd Annual Meeting of the American Society of Clinical Oncology, held in May 1997, however, demonstrate that an oral antiemetic agent, granisetron hydrochloride (Kytril, SmithKline Beecham Pharmaceuticals), is as effective as an intravenous formulation, ondansetron hydrochloride (Zofran, Cerenex Pharmaceuticals).

Granisetron's oral formulation, according to Edith A. Perez, M.D., Mayo Clinic in Jacksonville, Fla., is the only oral agent approved for both moderately and highly emetogenic chemotherapy, an indication identical to that of IV formulations of granisetron and ondansetron. Both granisetron and ondansetron are serotonin (5-HT3) antagonists that block transmission of emesis signals to the brain by binding to serotonin receptors in the gut.

Perez was principal investigator of a trial involving 1,085 patients randomized to oral granisetron or IV ondansetron in conjunction with chemotherapy with cyclophosphamide or carboplatin. Five hundred forty-two patients were randomized to oral granisetron (2 x 1 mg given 60 minutes before chemotherapy) and 543 patients to IV ondansetron (32 mg infusion given 30 minutes before chemotherapy) along with cyclophosphamide- (500 to 1,200 mg/m^2) or carboplatin- (300 mg/m^2) based chemotherapeutic regimens. Prophylactic corticosteriods (dexamethasone and methylprednisolone) were administered during the study among 441/542 (81.4 percent) of the patients treated with granisetron and 443/543 (81.6 percent) of the patients treated with ondansetron.

Complete control of emesis during the first twenty-four hours after chemotherapy was reported in 71 percent of oral granisetron-treated patients and in 72.6 percent of the IV ondansetron-treated patients. Good control of nausea was reported for 60 percent for the oral agent vs. 58.4 percent for the IV agent. With the exception of significant differences in dizziness (9.6 percent for IV ondansetron vs. 5.4 percent for oral granisetron) and abnormal vision (4.2 percent for IV ondansetron vs. 0.6 percent for oral granisetron), no differences in the most common side effects (headache, constipation, and diarrhea) were observed between the two treatments, said Perez.

"The oral drugs are convenient, easy to use, have few side effects, and are less expensive than their IV counterparts," said Richard Gralla, M.D., director of the Ochsner Cancer Institute in New Orleans, La., the lead investigator of a second trial comparing oral granisetron to IV ondansetron.

In that trial, 1,054 patients receiving cisplatin chemotherapy were randomized to the same regimens as in the above-mentioned trial. Data analysis showed that 54.7 percent of patients taking oral granisetron and 58.3 percent of patients taking IV ondansetron had total control over nausea and vomiting. Side effects in this trial were also reported to occur at similar frequencies between treatment groups.

Beyond the convenience of the oral formulation, oral administration is less expensive than the intravenous route. Gralla estimated that a 2 mg oral dose of granisetron costs about $60 compared to approximately $130 for the IV ondansetron. "We can now protect the majority of patients from nausea and vomiting by administering a pill," he concluded.

According to investigators in both trials, concomitant steroid administration resulted in slightly better control of both nausea and emesis with each regimen. In Perez's trial, at twenty-four hours post-treatment, corticosteroid use increased the percentage of patients gaining total control of both nausea and emesis from 48.5 percent to 61.9 percent with oral granisetron treatment, and from 50 percent to 59.8 percent with IV ondansetron. Perez noted also that in both treatment groups, males experienced better control rates than did females. No gender analyses were done in the Gralla study.

"The major advantage," Perez stated, "is that patients no longer need to be connected to an IV."

—*Walter Alexander*

OXALIPLATIN PROMISING IN OVARIAN CANCER

Oxaliplatin, a novel type of platinum drug, has been shown to have activity against human ovarian cancer. Phase II and phase III data presented by French investigators at the 33rd Annual Meeting of the American Society of Clinical Oncology suggest potential clinical benefit from synergistic interactions of oxaliplatin with cisplatin. Cisplatin is the treatment of choice for advanced ovarian cancer, particularly in the setting of disease-resistant to conventional therapy.

Oxaliplatin is a prototype diaminocyclohexane (DACH) platinum compound that, like cisplatin and carboxyplatin, kills cancer cells by promoting interstrand DNA cross-linking. In addition, oxaliplatin differs significantly from conventional platinum agents in that its antitumor action also

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involves a mismatched DNA repair mechanism. Importantly, oxaliplatin has little overlapping toxicity with earlier platinum drugs —its only dose-limiting toxicity being a cumulative but reversible peripheral sensory neuropathy that is generally manageable by dose reduction or suspension. Thus, at least in the setting of ovarian cancer, it may be possible to combine oxaliplatin with conventional therapy given at full dose, without exacerbating any adverse effects.

More than 70 percent of patients with ovarian cancer have advanced-stage disease at diagnosis because the tumor remains symptomatically silent for long periods of time and because there are no reliable early diagnostic indicators for this disease. Despite recent improved clinical outcomes achieved using high-dose cisplatin—the gold standard—or incorporation of cyclophosphamide and paclitaxel into platinum-based regimens, about 80 percent of patients diagnosed with advanced disease fail therapy. Unlike cisplatin and carboplatin, oxaliplatin has no renal, hepatic, otic, or major hematologic toxicity. Hence, a number of European teams are exploring the potential benefit of incorporating this novel drug into cisplatin- or carboplatin-based regimens for treating advanced ovarian cancer.

Salvage therapy. An initial phase II trial of oxaliplatin salvage therapy yielded encouraging results in twenty-five patients with advanced ovarian cancer who had failed three or more prior chemotherapy regimens—including at least one platinum-based combination,[1] stated Jean Louis Misset, M.D., head of medical oncology at the Hôpital Paul Brousse in Villejuif and professor of oncology at the University of Paris. Adding oxaliplatin to cisplatin did not increase the overall response rate (about 40 percent) or median duration of response (about four months). However, Misset pointed out, three of thirteen patients who had become refractory to cisplatin achieved objective response upon addition of oxaliplatin to their prior therapy. Importantly, myelotoxicity was not increased by the addition of oxaliplatin to cisplatin, and the cumulative sensory peripheral neuropathy secondary to oxaliplatin was reversible within a few months of drug discontinuation.

The take-home message, Misset said, is that oxaliplatin has equivalent activity to cisplatin in both pretreated and previously untreated advanced ovarian cancer, and is tolerated better.

First-line therapy. Encouraged by these results, Misset and colleagues proceeded to a phase II/III trial conducted at twenty-six French centers to compare the safety and efficacy of oxaliplatin vs. cisplatin, given in combination with cyclophosphamide, as first-line therapy for 182 patients with newly diagnosed, previously untreated, advanced ovarian cancer.[2] Patients were randomized to receive six consecutive cycles of either oxaliplatin (130 mg/m^2, IV, q 3 wk) or cisplatin (100 mg/m^2, IV, q 3 wk), given in combination with cyclophosphamide (1000 mg/m^2, IV, q 3 wk). The two groups were matched for disease characteristics and known prognostic factors. Misset said that at median thirty-two-month follow-up, patients in the oxaliplatin and cisplatin arms had comparable rates of CR (34 percent vs. 40.5 percent), PR (15 percent vs. 12 percent), and overall objective response (51.5 percent vs. 65 percent), as well as comparable rates of median survival (20.9 vs. 26.2 months) and progression-free survival (11.9 vs. 13.2 months).

However, he pointed out, significant differences favoring the oxaliplatin arm were seen in the toxicity profile: Grade III-IV myelotoxicity requiring treatment delays were twice as frequent in the cisplatin as in the oxaliplatin arm (37 percent vs. 18 percent), while grade III-IV sensory neuropathy requiring cycle delays occurred in 2 percent of oxaliplatin-treated patients but in none of the cisplatin-treated patients.

The take-home message, Misset said, is that oxaliplatin has equivalent activity to cisplatin in both pretreated and previously untreated advanced ovarian cancer, and is tolerated better.

—Lilian Delmonte, D.Sc.

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