Oxaliplatin With 5-FU or as a Single Agent in Advanced/Metastatic Colorectal Cancer

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No adequate second- or third-line therapy is available in the United States for patients with metastatic colorectal cancer and disease progression following treatment with fluorouracil (5-FU)-based therapy and an irinotecan (CPT-11, Camptosar) has resulted in further improvements in response rates and survival; however, median survival times range between 12 and 14 months.[2]

Single-agent oxaliplatin (Eloxatin) has demonstrated consistent but modest activity in metastatic disease that progressed after treatment with 5-FU-based therapy, achieving response rates of approximately 10%.[3,4] In previously untreated patients using a variety of oxaliplatin/5-FU/leucovorin schedules, response rates have been reported to be as high as 40% to 60%, with median survivals in excess of 15 months.[5,6]

In a phase II trial, André and coworkers treated 5-FU-refractory colorectal cancer patients with 5-FU/leucovorin plus oxaliplatin (this incorporated the 5-FU/leucovorin regimen on which the patients had previously progressed). Significant activity was observed, with patients achieving a 27% objective response rate and a 30% stable disease rate.[7] These data demonstrated that oxaliplatin appeared to add to the efficacy of a variety of 5-FU regimens in patients with refractory disease.

Mechanism of Action

The putative mechanism of action of oxaliplatin is similar to that of cisplatin (Platinol) and other platinum compounds.[8-10] Oxaliplatin forms intrastrand platinum-DNA adducts/crosslinks between two adjacent nucleotide base pairs. The formation of these intrastrand crosslinks inhibits such nuclear processes as DNA replication and transcription, resulting in cell death in actively dividing cells. Interstrand crosslinks are also formed but to a lesser extent.

Study Design

This multicenter, open-label, compassionate-use trial of oxaliplatin is being conducted at 44 centers in the United States and Canada. The objective is to provide oxaliplatin for compassionate use in patients who have had at least one prior chemotherapy regimen for locally advanced metastatic colorectal cancer, but who are ineligible for standard therapies.

The study population consists of patients with advanced adenocarcinoma of the colon or rectum who are not amenable to potentially curative treatment. Eligibility requirements are listed in Table 1. Patients were assigned to one of the six regimens described in Table 2.

All patients underwent a comprehensive pretreatment evaluation, including history, physical examination, assessment of Eastern Cooperative Oncology Group (ECOG) performance status (PS), and laboratory assessment to measure organ function. Interim evaluations performed to ensure
safety prior to administration of each cycle included a physical examination, toxicity assessment, and hematologic and chemistry studies. Dose modifications were made in the case of hematologic, gastrointestinal, neurologic, or skin toxicities. The planned duration of therapy was eight cycles of oxaliplatin, with further treatment requested for patients who required additional therapy after this period. Supportive therapy was given at the discretion of the investigator or treating physician.

**Results**

As of June 1999, 1,131 patients had been enrolled. Patient characteristics are presented in Table 3. All patients had received prior therapy, with a mean of 1.9 cycles (see Table 4). The 5-FU regimen selected by the investigators and the mean time on therapy are given in Table 5. The recommended dose intensity of oxaliplatin was 43.3 mg/m²/wk, except for the high-dose regimen, in which the recommended dose intensity was 36.4 mg/m²/wk. Table 6 lists the dose intensity received by the patients.

Serious adverse events were categorized. On-study deaths occurred mostly as a result of disease progression, and study drug-related deaths accounted for less than 1% of mortality. Hospitalizations were associated mainly with disease state, and included bowel obstruction, deep vein thrombosis, surgical procedures, dehydration, and nausea and vomiting. The most frequently observed side effects of therapy included laryngeal dysesthesia, anaphylaxis, nausea, vomiting, diarrhea, dehydration, neutropenia, fevers, cramping, rigors, spasms, seizure, and altered mental status and syncope. Laryngeal dysesthesia, usually cold-induced, was readily reversible (following discontinuation of oxaliplatin therapy).

A peripheral sensory neuropathy was occasionally acute at onset, but was usually cumulative, rarely dose-limiting, and normally reversible with discontinuation of the drug. Diarrhea was usually controllable and rarely required hospitalization. Neutropenia and thrombocytopenia also rarely warranted additional therapy, but did account for dose delays. The reasons for removing patients from study are listed in Table 7.

Overall, oxaliplatin was well tolerated and offered significant benefits to a large group of patients. Time to off-study due to treatment failure (mostly progressive disease) was 3.5 months overall (2.8 months for the single-agent arm, and 3.6 months for the combination cohorts). Partial remissions and stabilization of metastatic disease were observed.[11]

**Conclusions**

For patients with metastatic colorectal cancer and disease progression after treatment with 5-FU and irinotecan chemotherapy, oxaliplatin offers an alternative treatment strategy. The agent is well tolerated and exhibits a manageable toxicity profile. This compassionate-use study is ongoing and data are still being collected.

**References:**


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