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Original Article

Assimilating Oxaliplatin (Eloxatin) into the Management of Colorectal Cancer

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Abstract

Oxaliplatin (Eloxatin) is a third-generation platinum analogue which is a novel compound with proven anti-tumor activity in colorectal cancer. That has demonstrated synergy with 5-fluorouracil (5-FU) in human tumor xenograft models. A series of phase II trials demonstrated that, as second-line therapy, oxaliplatin in combination with 5-FU/leucovorin (LV) is active and can overcome clinical resistance to 5-FU. Subsequently, two large, randomized, phase III trials demonstrated that the addition of oxaliplatin to 5-FU/LV significantly improved response rates and time to disease progression in the first-line setting, but had no statistically significant impact on survival. Oxaliplatin in combination with 5-FU/LV represents an important treatment option for patients in whom 5-FU-based therapy has failed and as first-line therapy. Oxaliplatin has also been investigated in combination with the oral Fluoropyrimidine, capecitabine. As an oral agent that exploits the high intratumoral activity of thymidine phosphorylase to generate 5-FU preferentially within tumor tissue, capecitabine may improve the efficacy and tolerability of Fluoropyrimidine/oxaliplatin combination therapy. A phase I dose-escalation study has been performed in patients with advanced/metastatic solid tumors to establish the most appropriate regimen. The study indicated that the combination is feasible and has substantial antitumor activity in patients with colorectal cancer. This article provides an overview of the clinical trial data for oxaliplatin and discusses how oxaliplatin may best be used in the future.

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Introduction

Oxaliplatin is a third-generation platinum analogue, with activity and safety profiles that differ from those of other platinum derivatives, including Cisplatin and Carboplatin [1]. Platinum compounds are thought to act through the formation of platinum-DNA adducts that inhibit DNA synthesis and repair, with cytotoxicity potentially enhanced by the induction of apoptosis through a different mechanism. Oxaliplatin contains a bulky carrier ligand within its structure, and forms DNA adducts that more effectively inhibit DNA synthesis and are generally considered to be more cytotoxic than those of either Cisplatin or Carboplatin.

Oxaliplatin in Second-Line Therapy

Preclinical studies demonstrated that, unlike other platinum compounds, oxaliplatin is active in colorectal cancer models and has synergistic activity with 5-fluorouracil (5-FU) [1, 2]. Phase II trials showed that i.v. oxaliplatin monotherapy is

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active as second-line treatment for colorectal cancer, achieving response rates of 10%-11% in patients refractory to or progressing after 5-FU-based therapy [3, 4]. Median progression-free survival was typically approximately 5 months and median survival of 8-9 months was reported. These results are similar to those obtained in phase II studies of Irinotecan monotherapy in the same clinical setting [5-10].

Oxaliplatin has also been evaluated extensively in combination with 5-FU/leucovorin (LV) as second-line therapy for colorectal cancer in a series of phase II trials [11-14]. These studies evaluated a range of regimens with differing dose and administration schedules, with 5-FU administered as a protracted (≥24-hour) flat or chronomodulated infusion plus LV, with or without i.v. bolus 5-FU. The combination treatment showed higher efficacy than 5-FU/LV alone, with objective response rates of 21%-48% in 5-FU-pretreated patients, median progression-free survival ranging from 5 to 9 months and median overall survival ranging from 11 to 18 months.

These studies also demonstrated that the addition of oxaliplatin to 5-FU/LV can partially overcome clinical resistance to 5-FU. The efficacy of this combination may be explained in part by the synergistic activity of oxaliplatin and 5-FU seen in preclinical models [1].

Oxaliplatin in First-Line Therapy

The activity of oxaliplatin/5-FU/LV combination therapy in phase II trials in the second-line setting led to the initiation of two large, randomized, phase III trials investigating the same combination as first-line treatment for colorectal cancer. The primary endpoint in both studies was progression-free survival. One study evaluated oxaliplatin 85 mg/m^2 as a 2-hour infusion on day 1 only infused in parallel with LV 200 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and a 22-hour infusion of 5-FU 600 mg/m^2 on days 1 and 2 every 2 weeks [15]. The second study evaluated oxaliplatin 125 mg/m^2 as a 6-hour infusion on day 1 followed by chronomodulated 5-FU/LV (5-FU 700 mg/m^2 plus LV 300 mg/m^2 as 12-hour infusions, peaking at 04:00 hours on days 1-5) in a 3-weekly regimen [16]. In both studies, the treatment arms were well balanced for most prognostic factors, including performance status and number of metastatic sites at baseline. However, in the combination arm, a significantly higher proportion of patients had previously received adjuvant chemotherapy and significantly more patients had carcinoembryonic antigen (CEA) levels ≤10 mg/ml.

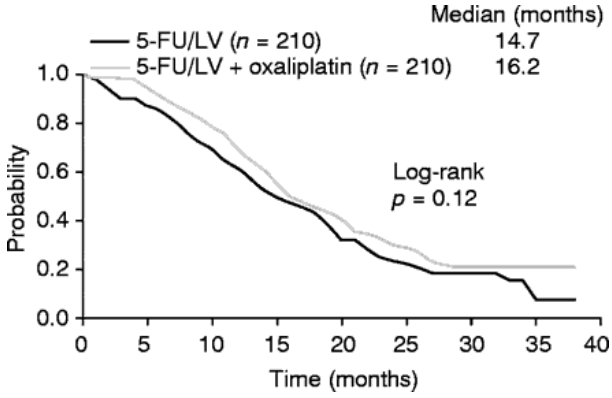

Figure 1: First-line oxaliplatin plus 5-FU/LV (de Gramont regimen) versus 5-FU/LV: overall survival

In the study [15], the addition of oxaliplatin to 5-FU/LV therapy significantly increased the tumor response rate (51% versus 22% with 5-FU/LV alone; $p < 0.001$) and median progression-free survival (9.0 versus 6.2 months; $p = 0.0003$). The effect of oxaliplatin on survival may have been obscured by effective post-study chemotherapy (57% of patients in the 5-FU/LV arm received post-study oxaliplatin/5-FU/LV) and surgical removal of metastatic lesions in a high proportion of patients in the control arms. In the trial, patients in the control arm experiencing disease progression could cross over to receive 5-FU/LV with oxaliplatin and consequently, second-line chemotherapy (oxaliplatin and/or Irinotecan) was administered to more than half of the patients originally randomized to the control arm.

Patients receiving first-line oxaliplatin with bolus-plus-infusion 5-FU/LV experienced a significantly higher incidence of grade 3/4 neutropenia, neurotoxicity, diarrhea, vomiting, and mucositis compared with patients receiving 5-FU/LV alone. First-line oxaliplatin with chronomodulated 5-FU/LV demonstrated a different safety profile:

grade 3/4 neutropenia was rare (2% of patients), although long-lasting Paresthesia occurred in 45% of patients and led to treatment withdrawal in 10% of cases. Oxaliplatin plus chronomodulated 5-FU/LV was associated with a significantly ($p \leq 0.01$) higher incidence of grade 3/4 diarrhea (43% versus 5%), nausea/vomiting (25% versus 2%), and treatment withdrawals (13% versus 1%) compared with 5-FU/LV alone.

The predominant toxicity with oxaliplatin is peripheral sensory neuropathy, of which there are two general types. Acute sensory neuropathy is exacerbated by cold temperatures (e.g., laryngopharyngeal dysesthesia) and is completely reversible. Chronic sensory neuropathy is frequent and cumulative, occurring in most patients after 24 weeks of treatment. Chronic sensory neuropathy slowly reverses after treatment is discontinued, and this side effect represents a dose-limiting toxicity. However, as grade III cumulative neurotoxicity generally occurs after 4 months of treatment, this toxicity is only relevant in patients who respond to therapy and not to those who withdraw owing to progressive disease. Studies are investigating whether the incidence of neurotoxicity can be reduced by modification of the schedule or the use of calcium and magnesium infusions or Carbemazepine.

A preliminary analysis of safety after 8-9 months of therapy revealed low incidences of grade 3/4 sensory neurotoxicity that were predominantly cumulative in nature (5% in the oxaliplatin/5-FU/LV arm and 0% in the Mayo Clinic regimen arm). The oxaliplatin/5-FU/LV arm was also associated with a low incidence of grade 3/4 diarrhea (6%), grade 3 mucositis (1%), and nausea/vomiting (4%). There have been no reports of grade 4 mucositis or nausea/vomiting. The response rates are similar to those reported in the previous phase III trials: 51% in the oxaliplatin/5-FU/LV arm and 22% in the Mayo Clinic regimen arm, with no overlap in confidence intervals. Moreover, progression-free survival is significantly different ($p = 0.0001$) between the two treatment groups: 8.0 months in the oxaliplatin/5-FU/LV arm and 5.6 months in the Mayo Clinic regimen arm. Survival data are not yet available. Therefore, modifying the schedule of oxaliplatin/5-FU/LV may reduce toxicity while maintaining efficacy.

Oxaliplatin in combination with 5-FU/LV is therefore an effective treatment for patients with metastatic colorectal cancer and represents an important option for patients in whom 5-FU-based therapy has failed. Further investigations are required to identify the optimal treatment regimen and to determine the true benefit, particularly in terms of survival, of this agent in colorectal cancer.

In addition, combination therapy in the first-line setting may be optimized if patient subgroups most likely to derive the greatest benefit from combination therapy can be identified, as discussed in the previous article. Indeed in the one study, patients with a higher concentration of serum alkaline phosphatase derived less benefit from oxaliplatin/5-FU/LV, and the survival difference became significant when the study population was stratified according to serum alkaline phosphatase. The efficacy and tolerability of second-line oxaliplatin in patients treated with 5-FU/LV in the phase III studies poses the question of whether a sequential approach to colorectal treatment is not an equally valid option. In this case, oral capecitabine would provide an ideal first-line therapy that could be followed by second-line treatment with oxaliplatin, as a single-agent or in combination with 5-FU/LV.

Capecitabine plus Oxaliplatin:

Capecitabine is a convenient oral Fluoropyrimidine that exploits the high intratumoral activity of thymidine phosphorylase to generate 5-FU preferentially within tumor tissue. Therefore, capecitabine may represent a more effective, better-tolerated, and more convenient alternative to 5-FU as a combination partner for oxaliplatin, while still potentially exploiting the synergy achieved with 5-FU.

An open-label, phase I [18], dose-finding study has investigated capecitabine in combination with oxaliplatin in 23 patients with advanced/metastatic solid tumors, all of whom had exhausted standard therapeutic options. Patients received oral

capecitabine 500-1,250 mg/m^2 twice daily on days 1-14 plus a fixed dose of oxaliplatin 130 mg/m^2, administered as a 2-hour i.v. infusion on day 1, in a 21-day treatment cycle. The primary objective of the study was to determine the maximum tolerated dose of capecitabine in combination with oxaliplatin, which was defined as that causing dose-limiting toxicities in one-third or more of a six-patient cohort during the first treatment cycle. Dose-limiting toxicities were defined as any clinically relevant grade 3/4 toxicity that did not resolve within 2 days of onset in the first treatment cycle, prolonged granulocytopenia (grade 4 for >5 days), or granulocytopenia with complications. Secondary objectives included evaluation of the safety profile and antitumor activity of the combination [18].

All patients had histologically confirmed advanced/ metastatic cancer that was unresponsive or untreatable with standard chemotherapy, but had a Karnofsky Performance Score ≥70% and a life expectancy of more than 3 months. Of the 23 patients, nine had colorectal cancer. Other tumor types included gall bladder, renal, and lung cancers (two patients each).

The principal dose-limiting toxicity was diarrhea, and the maximum tolerated dose was reached at the capecitabine 1,250 mg/m^2 dose level. Consequently, a further six patients were recruited at the capecitabine 1,000 mg/m^2 dose level. The dosing schedule recommended for phase II evaluation is therefore a 21-day treatment cycle of oral capecitabine 1,000 mg/m^2 twice daily (days 1-14) and i.v. oxaliplatin 130 mg/m^2 (day 1).

Incidence of dose-limiting toxicities (DLT) in the dose-finding capecitabine plus oxaliplatin trial patients received an average of 4.6 treatment cycles, and capecitabine/oxaliplatin combination therapy was well tolerated at dose levels below the maximum tolerated dose. The most frequent treatment-related adverse events in all treatment cycles were gastrointestinal and neurologic toxicities, and the majority of adverse events were of mild to moderate intensity. Severe (grade 3/4) laboratory abnormalities were rare. Grade 3 and 4 neutropenia occurred in only one patient each and grade 3 thrombocytopenia occurred in two patients. One patient experienced recurrent grade 3/4 hyperbilirubinemia, but this did not require treatment modification.

Capecitabine/oxaliplatin combination therapy demonstrated promising antitumor activity. Objective tumor responses occurred in five of nine patients with colorectal cancer, with disease stabilization observed in a further three patients with colorectal cancer. In addition, one patient with carcinoma of the gall bladder achieved an objective tumor response. The antitumor activity in the patients with colorectal cancer is particularly impressive, as all patients had previously received a 5-FU-containing chemotherapy regimen and four of the five responding patients had experienced tumor progression during or following therapy with Irinotecan.

These promising results have led to the initiation of a phase II study that is evaluating the safety and efficacy of the recommended regimen of capecitabine plus oxaliplatin as first-line therapy for metastatic colorectal cancer.

Conclusions

Oxaliplatin in combination with 5-FU/LV is an effective treatment option in the first and second line for patients with advanced colorectal cancer. As first-line therapy for colorectal cancer, oxaliplatin plus 5-FU/LV achieves superior efficacy compared with 5-FU/LV alone in terms of response rate and progression-free survival. In both phase III studies, however, the addition of oxaliplatin failed to achieve a significant increase in overall survival, possibly because active second-line chemotherapy, including extensive crossover and surgical removal of metastatic lesions in a high proportion of patients may have obscured any impact of oxaliplatin on survival. The principal toxicities are neuropathy and diarrhea. Further investigations are required to identify the optimal treatment strategy, determine the true benefit of oxaliplatin in terms of survival, identify patient subgroups likely to derive the greatest benefit from the addition of oxaliplatin to 5-FU-based therapy, and evaluate its role in combination with other agents (e.g., triple combinations).

Another avenue of investigation that appears particularly promising is the use of oxaliplatin in

combination with the oral Fluoropyrimidine capecitabine. Capecitabine/ oxaliplatin combination therapy is feasible and exhibits promising antitumor activity, especially in patients with metastatic colorectal cancer. The recommended dosing schedule for further evaluation is capecitabine 1,000 mg/m^2 twice daily (days 1-14) with i.v. oxaliplatin 130 mg/m^2 (day 1) every 21 days.

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