Role of Calcium/Magnesium Infusion in Oxaliplatin-Based Chemotherapy for Colorectal Cancer Patients

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The combination of oxaliplatin plus fluorouracil/leucovorin is known as the FOLFOX regimen, and it has become a standard regimen for colorectal cancer (CRC), both as adjuvant therapy and as treatment for metastatic disease. Unfortunately, platinum-based chemotherapies also produce neurotoxicity as a side effect. Neurotoxicity is the most common dose-limiting toxicity of oxaliplatin, and it is one of the major causes for patients to stop receiving chemotherapy. It can manifest as either of two distinct syndromes: a transient, acute syndrome that can appear during or shortly after the infusion (~1%-2% of patients), and a dose-limiting, cumulative sensory neuropathy. Calcium/magnesium (Ca/Mg) infusions have been used to decrease the incidence of oxaliplatin-induced neuropathy. The actual utility of Ca/Mg infusions in this setting has been an interesting and controversial topic. They may reduce the severity of neurotoxicity, but some investigators have questioned whether they also will alter the efficacy of these chemotherapy regimens. In this paper, we review the clinical data concerning the usefulness of Ca/Mg infusions in reducing the incidence of oxaliplatin-induced neuropathy as well as their effect on responsiveness to chemotherapy.

The incidence of colorectal cancer (CRC) has been decreasing over the past 2 decades, from 66.3 cases per 100,000 population in 1985 to 46.4 in 2005. It is believed that the increases in screening have allowed early detection and removal of colorectal polyps before they progress to cancer. However, approximately 146,970 new cases of CRC (consisting of 106,100 cases of colon cancer and 40,870 cases of rectal cancer) were still expected to occur in 2009. This makes CRC the fourth most common malignancy behind lung, prostate, and breast cancer, and accounts for approximately 10% of estimated new cancer cases. In addition, the mortality rates from CRC have decreased over the past 2 decades. This decrease reflects declining incidences rates and improvements in early detection and treatment. However, an estimated 49,920 deaths from CRC were expected to occur in 2009, accounting for almost 9% of all cancer mortality.[1]

The lifetime risk of being diagnosed with colorectal cancer is about 5%, with 90% of cases occurring after age 50. The incidence is higher in patients with specific inherited conditions that predispose them to the development of CRC, such as familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer (Lynch syndrome), Peutz-Jeghers syndrome, and juvenile polyposis. In the United States, the median age at diagnosis of CRC is 71 years.[1,2] Even when metastatic, CRC is a highly treatable and potentially curable disease. Death rates from CRC have declined progressively since the mid-1980s in the United States and in many other Western countries. Two major factors are the evolving advanced technology to diagnose CRC in earlier stages, and the development of more effective adjuvant chemotherapies. However, survival rates are stage-dependent, and the stage of the tumor is an important prognostic indicator of survival in early colon cancer.[3,4] Average 5-year survival rates in colon cancer, by stage, are[4,5]:

- stage I (T1–2, N0): 92%
- stage II (T3–4, N0): 73%
- stage III (T1–4, N1–2): 56%
- stage IV (any T, any N, M1): 8%

Treatment of Colorectal Cancer

Management of colon cancer depends on the stage of diagnosis, but generally includes surgical resection and chemotherapy—alone or in combination with other modalities (eg, radiofrequency ablation). The development of adjuvant chemotherapy (anticancer drugs in addition to surgery or radiation) has been significant in prolonging the survival rate.[6,7] Fluorouracil (5-FU) was the initial chemotherapy proven to reduce mortality in the CRC patient.[8]
Later, it was found that adding leucovorin, a reduced folate, would increase the efficacy of 5-FU by increasing thymidylate synthetase inhibition and improving clinical outcomes.[9] Interest in adjuvant chemotherapy was revived in the late 1980s with reports that suggested a survival benefit from 5-FU-based combination regimens and by the discovery of modulators of 5-FU activity such as leucovorin and levamisole, an immunomodulatory agent.[10,11]

**Oxaliplatin-Based Chemotherapy**

In the late 1980s, oxaliplatin (Eloxatin) was found to have activity in advanced CRC, and it is the only platinum derivative with activity against advanced CRC.[12,13] It binds and cross-links strands of DNA, forming DNA adducts—thus inhibiting DNA replication and transcription.[14] Oxaliplatin also displays synergistic in vitro cytotoxicity with 5-FU against human colorectal cell lines. A potential mechanism for this synergism is the downregulation of thymidylate synthase by oxaliplatin, which thereby potentiates the efficacy of 5-FU.[14,15] The combination of oxaliplatin plus 5-FU/leucovorin is known as the FOLFOX regimen, and it has become a standard regimen for CRC, both as adjuvant therapy and as treatment for metastatic disease.[14,16,17]

The use of the FOLFOX regimen as adjuvant treatment for colon cancer was confirmed by the Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC). This study concluded that adding oxaliplatin to a regimen of 5-FU and leucovorin improves the adjuvant treatment of colon cancer. The investigators randomly assigned 2,246 patients who had undergone curative resection for stage II or III colon cancer to receive 5-FU alone or with oxaliplatin for 6 months. The primary endpoint was disease-free survival. The result showed that the rate of disease-free survival at 3 years was 78.2% in the group given 5-FU/leucovorin plus oxaliplatin vs 72.9% in the 5-FU/leucovorin–only group ($P = .002$).[18,19]

In metastatic disease, patients treated with FOLFOX had a response rate, time to disease progression, and overall survival time that were superior to those observed with other combination chemotherapies, including IFL (irinotecan plus 5-FU) or IROX (irinotecan plus oxaliplatin). These data support the use of oxaliplatin-based chemotherapy as the preferred first-line combination chemotherapy for metastasis colorectal cancer.[14,20,21]

**Side Effects of Oxaliplatin**

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<td><strong>Grading of Oxaliplatin-Induced Neurotoxicity</strong></td>
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Unfortunately, platinum-based chemotherapies also produce neurotoxicity as a side effect.[14] Neurotoxicity is the most common dose-limiting toxicity of oxaliplatin. The grading and severity of oxaliplatin-induced neurotoxicity is shown in Table 1.[22] It can manifest as either of two distinct syndromes: a transient, acute syndrome that can appear during or shortly after the infusion (around 1%–2% of patients), and a dose-limiting, cumulative sensory neuropathy (10%–15% of patients after a cumulative dose of 780–850 mg/m2).[14,23] This neurotoxicity is induced or exacerbated by cold and prolonged muscular contraction after a voluntary contraction, and it is one of the major causes for patients to stop receiving chemotherapy. However, patients with neurotoxicity have no signs or very mild signs of axonal degeneration on clinical neurophysiologic examinations and nerve biopsy study.[24,25] This means that oxaliplatin has a direct effect on the excitability of sensory neurons and muscle cells.[24-26] Several studies have been done to propose the possible explanation of the pathogenesis.

Biotransformation of oxaliplatin produces oxalate ions, which are able to chelate calcium. Calcium binds within the pore of the sodium channel and enhances the rate of closing of the activation gates of the voltage-gated sodium channel. Therefore, oxalate, acting as a calcium chelator, may interact with the sodium channel by chelating calcium and interfering with sodium channel activity, leading to a decrease of the channel deactivation rate, and thus increasing neuronal
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Calcium and Magnesium Infusion to Reduce Neurotoxicity

In 2004, Gamelin et al published a clinical trial and concluded that calcium and magnesium infusion significantly reduced the incidence and severity of peripheral neuropathy secondary to oxaliplatin. They administered 1 g of calcium gluconate (Ca) and 1 g of magnesium sulfate (Mg) as an infusion, 1 or 2 hours prior to the oxaliplatin infusion and soon after the oxaliplatin drip finished. In their retrospective cohort of 161 patients treated with oxaliplatin plus 5-FU/leucovorin for advanced colorectal cancer, the percentage of patients with grade 3 distal paresthesia was significantly lower in the Ca/Mg group (7% vs 26%, \( P = .001 \)). The study also reported less neuropathy in the Ca/Mg group at the end of the treatment (20% vs 45%, \( P = .003 \)).[25,30]

However, the CONcePT (Combined Oxalipatin Neurotoxicity Prevention Trial) study, a clinical trial of 160 patients who were given Ca/Mg infusion to reduce the neurotoxicity, was prematurely terminated in 2007 after it was ongoing for 2 years. The independent data monitoring committee found that the Ca/Mg infusion reduced the efficacy of the chemotherapy regimen. Based on their central radiology review, the response rate associated with oxaliplatin could be reduced up to 52% (18% vs 33%).[31-33] Another trial, from The North Central Cancer Treatment Group (NCCTG)—the N04C7 trial—also showed a positive result. Despite its early termination following the CONcePT study, this prospective, randomized and double-blinded trial that enrolled 106 patients treated with the FOLFOX regimen demonstrated that the Ca/Mg infusions delayed the time to onset of grade 2 sensory neural toxicity.[34]

Subsequently, Gamelin stated that Ca/Mg infusion has no impact on oxaliplatin efficacy. In 2008, he reported on the French multicenter Neuroxa study, a double-blind randomized study designed to prove the effect of Ca/Mg infusions for preventing oxaliplatin neurotoxicity. This study again found a significantly lower frequency and grade of oxaliplatin neurotoxicity in the group receiving Ca/Mg infusion (5% vs 24% grade 2 National Cancer Institute Common Toxicity Criteria, \( P < .001 \)).[27]

In early 2008, Hochster presented a new analysis that emerged from a central, blinded radiology review of scans in 139 patients enrolled in the CONcePT trial. Based on the central radiology review, the response rate favored patients treated with Ca/Mg. Although the difference was not statistically significant \( (P = .70) \), it contradicted the data monitoring committee’s analysis that had shut down the trial previously.[33]

Conclusion and Recommendations

Neuropathy caused by oxaliplatin alters patients’ quality of life and may result in the postponement or interruption of the administration of chemotherapy. Several studies concluded that adding Ca/Mg infusions would reduce the peripheral neuropathy induced by oxaliplatin.[31-33,35] In addition, current evidence suggests that Ca/Mg infusions do not affect the efficacy of oxaliplatin-based chemotherapy.[33] Since peripheral neuropathy is one of the main reasons for patients to stop chemotherapy, it may be reasonable to add Ca/Mg infusions as part of the chemotherapy regimen in a patient considering discontinuation of chemotherapy because of the development of neuropathy or in patients with preexisting neuropathy.

The role of Ca/Mg infusions has been controversial. It appears that giving Ca/Mg infusions prior to and after the oxaliplatin infusion will significantly reduce the neurotoxicity side effect. However, it is important to prove that Ca/Mg infusion is not decreasing the efficacy of the chemotherapy. A randomized, prospective clinical trial should be conducted to prove that the treatment would work as effectively with or without the addition of Ca/Mg infusion, as suggested in the re-analysis of the CONcePT trial. If it is proven that Ca/Mg infusions do not alter the efficacy of chemotherapy, it may be reasonable to add them to the standard oxaliplatin-based chemotherapy regimen, to lessen the incidence of neurotoxicity.

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References:

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