Marsden Centre
for Excellence In Integrative Medicine

**Colorectal Cancer: FOLFOX/FOLFIRI and Supportive natural therapies**

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## Introduction

In 2010, an estimated 22 500 Canadians were diagnosed with colorectal cancer and 9100 died from this disease. Overall, colorectal cancer is the second leading cause of cancer related deaths in men and women combined in Canada (Canadian Cancer Society 2010) and the United States. (American Cancer Society 2011)

Treatments for colorectal cancer include adjuvant and neoadjuvant application of chemotherapy. Preoperative chemotherapy is used to decrease the magnitude of resection needed, treat hepatic and systemic micro metastases, downsize colorectal metastases and apply liver resections in patients who would have been unresectable without positive response to neoadjuvant chemotherapy. (Zorzi 2007)

There are various chemotherapeutic regimens available. Folinic acid (FOL) is usually combined with fluorouracil (F) and either irinotecan (IRI) or oxaliplatin (OX) to further improve response rates and prolong survival. Both combinations (FOLFIRI and FOLFOX) are approved as standard treatment for metastatic colorectal cancer. (Goldberg 2007) (Kono 2009) (Wrzesinski 2007)

Despite the notable improvements in overall survival with these therapies they are not without significant side effects. One of the largest concern for these conventional therapies include neurotoxic effects of oxaliplatin and which can become dose-limiting, (Kono 2009) (Kurniall 2010) (Nishioka 2011) leading to inability to finish prescribed regimens. In more than 90% of patients, oxaliplatin causes both a reversible cold-related dyesthesia and a dose-limiting chronic peripheral sensory neuropathy in 10-18% of patients after 4-6 months when the cumulative dose of oxaliplatin approaches 800mg/$m^2$. (Milla 2009)

In a majority of cases where these chemotherapeutic regimens produce a response, virtually all responses are incomplete and emergence of resistance and recurrence of cancer is universal. (Patel 2010) The question then becomes what can be done to improve patient tolerability and success of these conventional regimens to maximize outcomes for patients.

## FOLFOX

### Calcium and Magnesium

Calcium and magnesium infusions appear to significantly reduce the severity and incidence of peripheral neuropathy due to oxaliplatin and thus allow for better treatment outcomes through the decreased rate of withdrawal as a result of unbearable chemotherapeutic side effects.

A retrospective cohort trial by Gamelin et al. (2004) included 161 patients treated with FOLFOX for advanced colorectal cancer with three regimens of oxaliplatin (85mg/$m^2$, 100mg/$m^2$ and 130mg/$m^2$). 96 patients received infusions of one gram each of calcium gluconate (Ca) and magnesium sulfate (Mg) one to two hours before and soon after oxaliplatin infusion (Ca/Mg group). The control group consisted of 65 patients who did not receive these Ca/Mg infusions. In this study, Ca/Mg infusions appear to reduce the incidence and intensity of acute oxaliplatin-induced symptoms and may delay cumulative neuropathy, especially in 85mg/$m^2$ oxaliplatin dosage. The percentage of patients with grade 3 distal paresthesia was lower in the Ca/Mg group (7% versus 26%, P=0.001). In the 85 mg/$m^2$ oxaliplatin group, patients with grade 2 and 3 recovered significantly more rapidly from neuropathy than patients without Ca/Mg. 20% of patients in Ca/Mg group had neuropathy versus 45% (P=0.003) at the end of the treatment. Significantly fewer patients stopped treatment for toxicity (any type) in the Ca/Mg group compared with the control (33% versus 51%, P<0.02). Only 4% of patients withdrew for neurotoxicity in the Ca/Mg group versus 31% in the control group (P=0.000003). The tumor response rate was similar in both groups. Treatment efficacy after 3 months of treatment was also evaluated. In order to have two homogeneous populations in respect to number of patients, data was collected only in the 130mg/$m^2$ group. In the group with Ca/Mg, the response rate (best response) was 45% compared with 35% for the control group. Ca/Mg infusions did not decrease treatment efficacy after three months of treatment. (Gamelin 2004) The mechanism of action of Ca/Mg infusions appears to occur through their action as potential oxalate chelators. (Gamelin 2004) Once transformed in the body, oxaliplatin produces oxalate ions which are able to chelate calcium. Calcium binds within the pore of the sodium channel and prolongs the rate of closing of the activation gates of the voltage-gated sodium channel. By chelating calcium, oxalate may interact with the sodium channel and thus interfere with sodium channel activity increasing neuronal hyperexcitability. (Kurniall 2010)

Another study named the Combined Oxaliplatin Neurotoxicity Prevention Trial (CONcePT) was designed to optimize the use of FOLFOX with bevacizumab as first-line therapy for patients with advanced colorectal cancer. The word “combined” referred to the fact that Ca/Mg would first be used in a placebo-controlled comparison to decrease oxaliplatin-induced neurotoxicity and then using different chemotherapy scheduling options (continuous versus intermittent use of oxaliplatin). The Data Monitoring Committee halted the CONcePT trial in May 2007. A review by this independent data monitoring committee found that data from the 174 patients analyzed from this trial appeared to show that patients

who received calcium and magnesium had a lower response rate than the placebo group. (Grothey 2008) (Hochster 2007)

In June 2007, a phase III, two arm, randomized, placebo-controlled, double-blind, National Cancer Institute sponsored cancer control trial, N04C7, was terminated early due to the committee's report on the CONcePT study. Preliminary data demonstrated that Ca/Mg infusions delayed time to onset of grade 2 sensory neural toxicity National Cancer Institute Common Terminology Criteria for Adverse Events (NCT CTCAE; version 3) criteria. (Nikcevich 2008) At the time of closure 104 patients had been randomly assigned and 102 had started study medication (n=50, Ca/Mg; n=52, placebo). A subsequent independent, blinded radiologic review of radiologic scans from 139 patients enrolled in the CONcePT trial, demonstrated that the antitumor response rate was numerically lower in the group receiving placebo versus the group receiving Ca/Mg. The response rate thus favored those treated with Ca/Mg. While the difference was not statistically significant (P=0.70) it nonetheless contradicted previous data presented by the monitoring committee. (Grothey 2008) (Hochster 2008) This pointed to an obvious mistake in closing multiple studies on Ca/Mg based on the committee's findings and showed possible credibility of this therapy in the reduction of FOLFOX side effects.

Results from Grothey et al.'s (2011) analysis are based on the early terminated N04C7 trial on 102 patients that had initiated study medication with data cutoff done after 127 days (due to study closure). Patients with colon cancer undergoing adjuvant FOLFOX therapy were randomly assigned to Ca/Mg (1g each) 30 minutes pre and post oxaliplatin or placebo in a double blind manner. Ca/Mg decreased the incidence of chronic, cumulative, grade 2 or greater sensory neurotoxicity (sNT), as measured by NCI CTCAE (22% v 41%, P=0.038) and also by oxaliplatin-specific sensory neurotoxicity scale (28% vs 51%, P=0.018). In addition, acute muscle spasms associated with oxaliplatin were significantly reduced (P=0.01). No effect on acute, cold-induced sNT was found. No substantial differences in adverse effects were noted between Ca/Mg and placebo. (Grothey 2011) Ca/Mg infusions thus appear to decrease oxaliplatin-mediated chronic, cumulative sensory neurotoxicity. (Grothey 2011)

**Curcumin**

Curcumin, the major active ingredient of turmeric (Curcuma longa) with no discernible toxicity in multiple human studies, inhibits the growth of transformed cells and has been shown to suppress initiation, promotion and progression of colon carcinogenesis in carcinogen-induced rodent models. (Shishodia 2007) In a phase I clinical trial, curcumin was found to be effective in inhibiting the growth of a variety of tumors. (Sharma 2004)

FOLFOX produces an incomplete response resulting in survival of cells that may lead to cancer recurrence. Inclusion of curcumin in conventional chemotherapy

regimens could be an effective strategy to prevent emergence of chemoresistant colon cancer cells. (Patel 2007)

Evidence suggests that the development and progression of many malignancies, including colorectal cancer, are associated with activation of multiple signaling pathways that are responsible with the inhibition of apoptosis, promotion of proliferation and induction of metastasis. A large body of evidence suggests that epidermal growth factor receptor (EGFR) and its family members, especially ErbB-2/HER-2 and ErbB-3/HER-3 (collectively referred to as EGFR's) play a crucial role in regulating several pathways that affect tumor cell survival, angiogenesis, motility and invasiveness. (Messa 1998) In particular, overexpression of EGFR and HER2 in colorectal cancer correlates with an extremely poor clinical prognosis. (Patel 2010) Recent data have also implicated insulin-like growth factor and insulin-like growth factor receptor 1 (IGF/IGF-1R) system in the development and progression of colorectal cancer. (Adachi 2002) (Patel 2010) Therefore agents that target EGFRs and IGF-1R are likely to affect multiple aspects of tumor progression. (Patel 2007)

In an in vitro study by Patel et al. (2007), a combination of curcumin with FOLFOX was found to produce a significantly greater inhibition ($p<0.01$) of growth and stimulated apoptosis ($p<0.001$) of colon cancer HCT-116 and HT-29 cells than that caused by curcumin, 5-FU, curcumin+5FU, curcumin + oxaliplatin or FOLFOX alone. These changes were associated with decreased expression and activation (tyrosine phosphorylation) of EGFR, HER-2, HER-3 and IGF-1R. (Patel 2007) While curcumin, 5-FU, curcumin + 5-FU and FOLFOX alone were all effective in significantly inhibiting the growth of HCT-116 or HT-29 cells by 33-60%, the combination of curcumin and FOLFOX was found to cause a 68-73% inhibition of growth when compared with controls. Curcumin when combined with FOLFOX inhibited both expression and activation of EGFR, HER-2 and HER-3 in HCT 116 cells to a much greater extent (72%-100%) than that caused by each agent/regimen alone. Thus synergistic inhibition of growth with curcumin and FOLFOX combination may be due to decreased activation of EGFRs and IGF-1R and their subsequent signaling. (Patel 2007)

In 2010, an in vitro study was conducted to study FOLFOX alone and in combination with 25uM or 50uM of curcumin. 60-70% of cells survived following 48 h incubation with FOLFOX. Chemotherapy surviving cells were then placed for 48 hours of FOLFOX, FOLFOX+25uM curcumin or FOLFOX+50uM curcumin treatment. Further treatment of chemo surviving cells with FOLFOX showed growth inhibition of 16-27% while treatment of chemo surviving cells with FOLFOX+curcumin 25uM produced 60% growth inhibition and 70-80% inhibition in that with 50uM of curcumin. (Patel 2010)

A growing body of evidence lends support to the concept that epithelial cancers including colorectal cancer are driven by self-renewing cells called cancer stem cells (CSC) that are distinct from most of the cells in the tumor. (Yu 2009) These

CSCs are thought to be capable of self-renewal, able to multiply, invade and metastasize. Therefore, failure to eliminate these CSCs may be one of the underlying causes for recurrence of malignancy. (Yu 2009) In an in vitro study by Yu et al. (2009), higher levels of CSC's in FOLFOX treated colorectal cancer cells as well as increased EGFR expression was seen. Colon CSCs have been shown to express surface markers CD44, CD166, CD133 and epithelial-specific antigen. Treatment of FOLFOX-surviving cancer cells with either curcumin alone or together with FOLFOX resulted in a marked reduction in CSC's as evidenced by the decreased expression of CD44 and CD166 as well as EGFR and by their ability to form anchorage-dependent colonies. (Dick 2008) Curcumin by itself or together with conventional therapeutic could be an effective treatment strategy for preventing the emergence of chemoresistant colon cancer cells by reducing or eliminating CSCs. (Yu 2009).

**Glutamine**

In a study by Wang et al. (2007), 86 patients with metastatic colorectal cancer treated with FOLFOX were randomized to receive 15g of glutamine twice a day for seven days every two weeks starting on the day of oxaliplatin infusion (n=42,) or to be in the control group (n=44). A lower percentage of grade 1-2 peripheral neuropathy was observed in the glutamine group (16.7% vs. 38.6%, p=0.04) after two cycles of treatment and significantly lower incidence of grade 3 and 4 neuropathy was noted in the glutamine group after four cycles (4.8% vs 18.2% p=0.05) and six cycles (11.9% vs 31.8%, p=0.04). By adding glutamine, interference with activities of daily living was lower (16.7% vs 40.9%, p=0.02) and need for oxaliplatin dose reduction was lower (7.1% vs 27.3%, p=0.02%). There were no significant between-group differences in response to chemotherapy (52.4% vs 47.8%, p=0.9), electrophysiological abnormalities, grade 3-4 non-neurological toxicities ie. grade 3-4 leukopenia, thrombocytopenia, liver and renal function (26.2% vs 22.8%, p=0.76) or survival. Oral glutamine seems not to affect treatment response of oxaliplatin-based chemotherapy or survival for these patients. Oral glutamine appears to significantly reduce the incidence and severity of peripheral neuropathy of metastatic colorectal cancer patients receiving oxaliplatin without affecting response to chemotherapy and survival. (Wang 2007)

**Glutathione**

In a study by Milla et al (2009), 27 patients were included who were to have FOLFOX treatments after curative resection of colorectal cancer with a maximum of 12 cycles. Patients were randomized to receive 1500mg/$m^2$ in 100mL of saline over a 15 minute period immediately before each oxaliplatin administration to glutathione (GSH) group or saline to the control group. The mean total oxaliplatin dose per patient was 841mg/$m^2$ in the GSH arm and 772 mg/$m^2$ in control arm. The GSH arm observed only moderate neurotoxicity with grade 1 in 7 patients (50%) and grade 2 in 7 patients (50%), whereas moderate to severe

neurotoxicity with grade 2 was seen in 9 patients (69%) and grade 3 in four patients (31%) in the placebo arm. No grade 4 neurotoxicity was observed in the two arms. At end of treatment cycles, patients in the GSH arm showed statistically significant reduction of neurotoxicity (P=0.0037) compared with placebo arm. There were no significant differences in the main pharmacokinetic parameters between the two arms. These findings indicate that coadministration of GSH is an effective strategy to reduce the oxaliplatin-induced neurotoxicity without impairing the pharmacokinetics of oxaliplatin. (Milla 2009)

Mechanistically, GSH administered intravenously is rapidly removed from the plasma compartment but is not taken up by most of the cells and probably even by the tumor cells except for those tissues requiring high concentrations of antioxidant species. (Leone 1992) High concentrations of GSH are found in the kidney (Zunino 1989) and in cells strongly exposed to reactive oxygen species such as those in the central and peripheral nervous system. (Dringen 2000, Philbert 1991, Philbert 1995) This distribution could explain the protective effect of GSH against neurotoxicity induced by oxaliplatin.

**FOLFIRI**

**Eicosapentaenoic acid (EPA)**

In a phase II trial, patients with advanced colorectal cancer having one prior chemotherapy regimen received 480ml of EPA oral nutritional supplement daily (16g protein, 1.09 g EPA, 0.46g DHA). (Read 2007) For 3 weeks before commencing their FOLFIRI rounds and continued 3 cycles of treatment for a total of 9 weeks. 23 patients enrolled to the trial, 20 completed 3 weeks, 15 completed 9 weeks. There was a significant increase in mean weight (2.5kg) at 3 weeks (p=0.03) and lean body mass was maintained. A significant increase was seen in energy levels (p=0.03) while all other quality of life (QOL) measures were maintained. Mean C-reactive protein increased by 14.9mg/L over the first 3 weeks (p-0.004) but decreased to baseline levels by the end of the trial. (Read 2007) A pro inflammatory state, present in advanced cancer patients is readily identified by elevations in acute phase proteins like C-reactive proteins. Elevated CRP can predict poorer survival in patients with colorectal cancer. (Nozoe 1998) Dietary counseling and provision of EPA may result in maintenance of nutritional status and QOL, however randomized trials are required to evaluate the impact of EPA on toxicity from chemotherapy. (Read 2007) Another important factor is that diarrhea occurs in 20-25% of patients receiving irinotecan for the treatment of CRC although it varies with the schedule of administration. A greater percentage of patients who did not comply with taking EPA experienced CTC grade 3 diarrhea compared with those who did comply, however no firm conclusions can be made due to the small number of patients. (Read 2007)

**FOLFOX/FOLFIRI**

**Glycine**

Glycine, a simple amino acid, has been shown to be protective against hepatic injury in various models and in clinical liver transplantation. It is also an essential component of glutathione and is thus needed for detoxification processes and has indirect effects as a radical scavenger (Zhong 2003, Luntz 2005). The regular human diet contains about 2g of glycine (Luntz 2005). Up to 90 g of glycine/day has been used in clinical trials over several weeks without any reported serious adverse effects (Heresco-Levy 1999, Luntz 2005). While in humans the normal serum level of glycine is approximately 300uM, increasing glycine intake to such a high level increases blood levels to more than 900uM (Heresco-Levy 1999). Patient's preconditioning with glycine before chemotherapy could reduce hepatic toxicity preventing microvascular changes such as atrophy of hepatocytes, steatosis, and/or hepatic necrosis. Glycine could also decrease the risk of surgery by preventing hepatic injury. Perioperative and postoperative complications could be decreased with better liver function.

Neoadjuvant chemotherapy is increasingly used to reduce the size of the resection required as well as postoperative tumor positive margins and to treat hepatic and systemic micro metastases. It also helps to apply liver resections in patients who would have been irresectable without neoadjuvant chemotherapy. Especially after irinotecan, hepatic steastosis and steatohepatitis can impair postoperative liver regeneration and may cause hepatic insufficiency after resection have been identified. Furthermore, hepatic sinusoidal dilatation is associated with oxaliplatin, which may lead to significant blood loss during surgery. There is a significantly increased incidence of nonalcoholic steatohepatitis in patients with either oxaliplatin or irinotecan compared to patients who had fluorouracil alone or no neoadjuvant chemotherapy. Prevention of chemotherapy-associated liver injury would lead to better liver function and thus allow a more aggressive resection. Fatty changes, which are unspecific markers of liver injury are known to appear after chemotherapy and are associated with increased postoperative morbidity. (Mikalauskas 2011)

Mikalauskas et al. (2011), completed an animal trial in a randomized, controlled, double blind fashion. In this trial 20 rats each were placed in a FOLFOX, FOLFIRI and control group respectively. A glycine rich diet was started five days before chemotherapy regimens. Those rats who were on a 5% glycine and 15% casein diet versus the 20% casein diet control had significantly decreased transaminases after chemotherapy regimens to 25-50% of control values. The optimal concentration of dietary glyceine for hepatoprotection is 5% in various models. A concentration of 5% dietary glycine has been shown to increase serum glycine levels four- to five fold.. (Mikalauskas 2011)

Results show that glycine appears to reduce aspartate aminotransferase (AST) and alanine transaminase (ALT) with respect to the control group and reduce Kupffer Cell (KC) activation. Chemo causes a hypermetabolic state and hypoxia in liver tissue, creating direct activation of Kupffer cells. Activated KCs release

vasoactive mediators, which impair hepatic microcirculation, leading to further hypoxia, damage and KC activation. Glycine is a strong inhibitor of liver macrophages and acts via a glycine-gated chloride channel, which subsequently inhibits Kupffer cell (KC) activation by decreased calcium inflow and thus stopping the aforementioned damaging cycle. Glycine also appears to prevent steatosis of the liver and improve microcirculation after chemo. Elevated serum transaminases, liver steatosis and decreased microcirculation are normally present after chemo. A disturbed hepatic microcirculation most likely is involved in the development of liver injury after chemotherapy. A glycine rich diet blunted all of the detrimental effects of chemotherapy concluding that glycine prevents chemotherapy-induced liver injury. (Mikalauskas 2011)

Another Section on Individual Chemotherapy studies

## CONCLUSION

While most trials explored have small study enrollment numbers and tend to mostly be in vitro or animal studies, their importance and findings cannot be ignored. Enhancement of chemotherapy treatments and reduction of toxic side effects for colorectal cancer patients must be explored further. The studies outlined in this review show that possibilities for promising combinations with FOLFOX and FOLFIRI exist and that these natural therapies may not only enhance chemotherapeutic actions but also reduce the likelihood of discontinued treatment due to intolerable side effects. The high occurrence of colorectal cancer and staggering cases of treatment shortcomings call for the utility of supportive treatments and more extensive research in this area.

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