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OXALIPLATIN-BASED THERAPY: STRATEGIES TO PREVENT OR MINIMIZE NEUROTOXICITY

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ABSRACT: Backbone: *Oxaliplatin is an anticancer drug used to treat some different neoplasms: lung, colorectal, ovarian, breast, head/neck, and genitourinary. Moreover, patients treated with oxaliplatin more often discontinue therapy due to peripheral neuropathy and not to tumor progression. Patient benefit is potentially compromising. Several strategies are been investigated to prevent neurotoxicity.*

Content: *In order to overcome this life-altering side effect, while taking advantage of the antineoplastic activities of the oxaliplatin, we detail recent findings of the , most common available strategies methods for prevention/minimize neurotoxicity. These include: a) variation of the standard scheduling; b) addition of various neurological drug to standard protocol; c) use of "natural" antioxidant agents.*

Summary: *Based on these actions, the oncologists will have a new issues with which to make treatment decisions for their patients to maximize benefit and minimize neurotoxicity. Based on this purpose, the clinician and pharmacists may join to evaluate advantages and limitation, in terms of costs and applicability, of the most appropriate strategies to incorporate routinely into clinical practice.*

Keywords: *Oxaliplatin-based therapy, Natural antioxidant, Dietary during cancer.*

INTRODUCTION

Toxicity profile of Oxaliplatin is well documented and often this adverse reaction leads to the suspension of therapy and potentially compromises patient benefit. Primarily toxicities include severe peripheral neuropathy linked to acute and cumulative doses of Oxalipaltin[1]. Current evidences have reported different polymorphisms associated to same adverse drug response[2]. However, since the clinical expertise to interpret pharmacogenomics data is low, the clinical application of these genetic variants remains unclear, and controversial[3]. In addition, emerging new evidences in nutrigenomics field, and new issues like stress and fatigue in cancer patients[4], suggesting an accurate evaluation of the diet during oxaliplatin therapy[5].

Several studies have suggested minimizing the neurotoxicity of oxaliplatin through the use of different compounds. These compounds include both

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natural substances and drugs. Specific examples include calcium and magnesium infusions, but they appear to reduce the effectiveness of chemotherapy, (moreover for someone calcium and magnesium do not prevent the neurotoxicity[6]). Furthermore, Guilongtongluofang is promising to prevent oxaliplatin-induced neurotoxicity in patients with colorectal cancer, but does not reduce the efficacy of oxaliplatin[7,8]. Altun ZS et al[9] have suggested that also Acetyl-L-Carnitine (ALC) could be an agent against cytotoxicity induced by cisplatin without interfering to therapeutic index. Already, since the year 2000, Conklin KA had proposed the use of antioxidant molecules to minimize the adverse side effects of chemotherapy[10].

Pharmacological approaches include neurological drugs primarily as venlafaxine and Duloxetine[11], suitable for concomitant infusion with oxaliplatin.

The aim of this review is to provide information for the oncologist on the advantage and limitations, of the most common available strategies methods for prevention toxicity by improving the best scheduling approach to minimize cumulative toxicity. Perhaps, to this end, it might be possible to even consider a personalized diet[12].

Metabolic fate of oxaliplatin and proposed model of toxicity

The cytotoxic lesion of platinating agents is primarily supposed to be the platinum intrastrand crosslink that forms on DNA, although treatment triggers a number of signal transduction pathways. Others proposed mechanism for oxaliplatin, including immunogenic signals for tumour cells before apoptosis, triggering Interferon gamma production and interaction with dendritic cells via Toll Like receptor4 resulting in death of cancer cells[13].

All platinating drugs get aquated when entering into a cell, losing chloride or oxalate ions. This positively charged molecule is then capable of interacting with nucleophilic molecules within the cell, as well DNA, RNA, and proteins. When the platinating agents binding to DNA ribbon the N7 atoms of the guanosine and adenosine nucleotide bases. Purine bases can form four different types of lesions on DNA: monoadducts, intrastrand crosslinks, and interstrand crosslinks and DNA-Crosslink[14]. The result is the contortion of the DNA. Than those formed from cisplatin or carboplatin, oxaliplatin adducts are bulkier and more hydrophobic. These features lead to different effects, which is likely contributing to the differences in toxicity[15]. The amount of DNA cross-links in neurons at a specified cumulative dose was significantly correlated with the level of neurotoxicity[16]. Patient trials of platinum agents have revealed that the seriousness of neurotoxicity is commonly cisplatin > oxaliplatin >> carboplatin. Cisplatin and oxaliplatin suffer hydrolysis to a greater extent than carboplatin, which can bring to the difference in the associated neurotoxicity severity patterns.

Oxaliplatin-based regimens

Despite a modest activity as a single agent, oxaliplatin exert significant activity in combination with other drugs especially used in combination with Fluoropirimidines[17]. Treatment in conjunction with 5-FU/LV (FOLFOX) have shown improved survival in the adjuvant setting among Stage III patients compared to 5-FU/ LV and 5-FU/irinotecan treatments[18]. Importantly, the incidence of low neurotoxicity associated with 5-FU, is increased with the addition of Oxaliplatin[19]. The *Food and Drug Administration* (FDA) noted that over 70% of the patients receiving oxaliplatin are involved by some degree of peripheral neuropathy[20], including ototoxicity and dysphonic syndrome[21]. Notably, neurotoxicity, and not tumor progression, is often the cause of treatment discontinuation. Despite these adverse life-altering side effects, Oxaliplatin therapy have a key role for the treatment choice in a large setting of cancer patients (pancreas, colon-rectum, lung, lymphoma etc); including in the so called frail patients (i.e. elderly and HIV-positive patients)[22-24] for whom the efficacy and especially the toxicity profile are important aspects[23,25].

STRATEGIES APPROACH FOR PREVENTION/ MINIMIZE OF CUMULATIVE NEUROTOXICITY

Several approaches have been optimized to prevent or minimize the cumulative neurotoxicity associated with Oxaliplatin therapy. These include interrupting and reintroducing oxaliplatin administration, lengthening the duration of infusion, various pharmacologic agents (i.e., calcium/magnesium, glutathione, etc.) and antioxidant "natural medicines".

Stopping and reintroducing oxaliplatin

When significant neuropathy develops during treatment, it is reasonable to discontinue the oxaliplatin and to switch to an oxaliplatin-free chemotherapy regimen allowing as much recovery as possible before reintroducing oxaliplatin. Many authors suggest that interspersing an oxaliplatin-free "maintenance"

regimen is a reasonable maneuver to prevent/minimize the development of neuropathy in responding patients who have received oxaliplatin-based therapy for 3-4 months with no clinically significant neuropathy. Data from the OPTIMOX-1 (maintenance with 5-FU/LV), OPTIMOX-2 (complete stop and restart of FOLFOX after 6 months)[26] and CONcePT trials (alternating schedule of 8 weeks mFOLFOX followed by 8 weeks of 5-FU/LV plus bevacizumab), suggest that this strategy decreases the risk of severe neuropathy without compromising antitumor efficacy[27]. However, continuous treatment with oxaliplatin is also an option in patients undergoing palliative chemotherapy for metastatic colorectal cancer, particularly in a responding patient with aggressive and/or bulky disease who is well tolerating the chemotherapy. In this setting, the chemotherapy-free intervals have the potential to worsen outcomes and are not recommended.

Lengthened infusion duration

Benefits from prolonging the duration of the infusion appears to be limited in preventing the acute neuropathy. The dose-limiting, cumulative neurotoxicity is not influenced by the duration of infusion or fractionation and is only dependent on the cumulative dose administered. Lengthening the duration of the oxaliplatin infusion from two to six hours has been evaluated in a randomized trial, in which 64 patients receiving adjuvant chemotherapy for colorectal or gastric carcinoma have been randomly assigned to six- or two-hour infusions of oxaliplatin[28,29]. The overall percentage of patients with sensory neurotoxicity has not been significantly decreased with the six-hour infusion (84% vs. 93% with the two-hour infusion), although there has been a significant decrease in the number of treatment cycles with grade 2 or greater neurotoxicity (6% vs. 19%).

The utility of this approach is limited by the logistical issues associated with a prolonged infusion, combined with the lack of effect on cumulative neurotoxicity.

Pharmacologic approaches

Several pharmacologic agents have shown properties to diminish the incidence and the severity of neurotoxicity either in small randomized trials or uncontrolled studies. Although initial results have been promising for these agents, appropriately randomized trials are required to confirm the neuroprotective effect of an intervention and to rule out any interference with antitumor activity before these pharmacologic approaches can be widely adopted.

A multitude of agents are suitable for concomitant infusions with oxaliplatin; these include, calcium and magnesium[30], Velafaxine[31], glutamine[32], neurotropin[33] and the Japanese traditional herbal formula Goshajinkigan (Gosha-Jinki-Gan)[34], and others (Table 1).

Benefits from **Calcium and magnesium infusions** have been demonstrated by placebo-controlled phase III trials in patients receiving oxaliplatin for metastatic colorectal cancer (the CONcePT trial) and in the adjuvant setting (the N04C7 trial[27] in patients with advanced disease[30]. However, a planned interim analysis of the first 180 patients enrolled in the CONcePT trial has found a significantly lower response rate in patients treated with Ca/Mg compared to the control group[35].

It is reasonable that the lower response rates in patients with metastatic colorectal cancer who received IV Ca/Mg in conjunction with oxaliplatin have not been established in subsequent preliminary reports detailing independent blinded central review of the response data from the CONcePT trial, or in a preliminary report of patients with metastatic disease who have been enrolled on the randomized French NEUROXO study.

In the CAIRO2 trial comparing *capecitabine*, *oxaliplatin*, and *bevacizumab* with or without *cetuximab*[36], the prophylactic use of Ca/Mg has been performed in 551 patients before and after the oxaliplatin infusion at least during the first treatment cycle with 369 (67%) receiving prophylaxis for all six oxaliplatin infusions while 181 have not received Ca/Mg during the first cycle. There has been a trend toward a lower incidence of all-grade late neurotoxicity with Ca/Mg (30% vs. 39%, $p = 0.07$), but with comparable incidence of grade > 2 neurotoxicity. While there has been significantly less all-grade acute neurotoxicity with Ca/Mg (81 vs. 91%), differences in the rates of ≥ grade 2 acute neurotoxicity have not been statistically significant (27% vs. 34%, $p = 0.06$).

In summary, these data suggest that supplemental Ca/Mg infusions may reduce some forms of neurotoxicity. However, there is still no strong data from an adequately powered prospective randomized study in advanced disease on which to base the assessment of the real value of the Ca/Mg infusions and their relationship to progression-free or overall survival.

Potential benefit from Venlafaxine has been suggested in a small placebo-controlled randomized trial conducted in 48 patients who developed distressing oxaliplatin-induced acute neurotoxicity[31]. Patients have been randomly assigned to venlafaxine 50 mg one hour prior to the oxaliplatin infusion followed by 37.5 mg twice daily from days 2 to 11 or placebo. The proportion of patients

TABLE 1. SEVERAL AGENTS ADDED TO OXALIPLATIN REGIMENS FOR MINIMIZE CUMULATIVE NEUROTOXICITY

Drug combination	Regimen	Effect	*Ref*
Ca^{2+} and Mg^{2+} s Infusion	FOLFOX 4	No found an impact of Ca^{2+} and Mg^{2+} infusions on oxaliplatin efficacy. Improved significant effect on oxaliplatin neuro-tolerance.	[29]
Venlafaxine	FOLFOX	A randomized trial of patients with acute Oxaliplatin-induced neurotoxicity receiving FOLFOX therapy, demonstrated a reduction in the proportion of patients with acute toxicity (31.3% in the placebo arm versus 5.3% in the venlafaxine arm, $p = 0.03$).	[30]
Glutamine	Oxaliplatin 85 mg/m², days 1 and 15 5-fluorouracil 500 mg/m² (weekly bolus) Folinic acid 20 mg/m² on days 1, 8, and 15 were given every 28 days as first-line treatment Glutamine 15 g twice a day for 7 consecutive days every	2 weeks starting on the day of oxaliplatin infusion A lower percentage of grade 1-2 peripheral neuropathy was observed in the glutamine group (16.7% vs. 38.6%) after two cycles of treatment, and a significantly lower incidence of grade 3-4 neuropathy was noted in the glutamine group after four cycles (4.8% vs. 18.2%) and six cycles (11.9% vs. 31.8%). There were no significant between-group differences in response to chemotherapy (52.4% vs. 47.8%), grade 3-4 non-neurological toxicities (26.2% vs. 22.8%), or survival in mCRC.	[31]
Neurotropin		The patients in the control group experienced significantly ≥ grade 2 and ≥ grade 3 neurotoxicity than those in the neurotropin group (70 vs. 21%, for at least grade 2 neurotoxicity, $p = 0.001$; and 39 vs. 2.7%, for at least grade 3 neurotoxicity, $p < 0.001$). In stage II and III of colorectal cancer	[32]
Glutathione	Oxaliplatin 100 mg/m² i.v. LV/ 5-FU 1,500 mg/m² i. v. over 24 h for 2 days (cycles repeated every 2 weeks)	Appears to diminish the accumulation of oxaliplatin in dorsal root ganglia in the mCRC.	[36]
Curcumin	Oxaliplatin 4 mg/kg Cisplatin 2 mg/kg Oral curcumin (10 mg/kg, 4 days before the platinum drug, and thereafter, concomitantly with it for 4.5 weeks)	Oral curcumin reversed the alterations in the plasma neurotensin (increased by specific tissue damage of scientific nerve) and sciatic nerve platinum concentrations, and markedly improved sciatic nerve histology in the platinum-treated rats	[39]
Ginkgo Biloba	Addition of Ginkgo Biloba 120 mg orally to FOLFOX CAPEOX	Ginkgo Biloba appears to decrease the intensity and duration of acute dysesthesias and may yield synergistic anti-tumor activity in Colorectal cancer.	[40]
Goshajinkigan (GJG) Kampo Medicines	FOLFOX6 (The cumulative dose of oxaliplatin was 1105 mg/m² for GJG group and 1120 mg/m² for control group) GJG 7.5 g/day of every day during mFOLFOX6 therapy	The incidence of grade 3 peripheral neuropathy in the GJG group was significantly lower than in the control group ($p < 0.01$). The incidence of grade 3 peripheral neuropathy after 10 courses was 0% in the GJG group and 12% in the control group, and after 20 courses was 33% in the GJG group and 75% in the control group. There were no differences in adverse effects between the two groups except for peripheral neuropathy and influence on tumor response in Non-resectable or recurrent colorectal cancer	[33]
Xaliproden	FOLFOX-4	Reduced grade 3 toxicity during treatment, but no clinically benefits are showed, after finishing treatment in Colon cancer	[42]
Carbamazepine	Oxaliplatin 85 mg/m² on days 1, 15 and 29 folinic acid 500 mg/m² 5-FU 2000 mg/m² on days 1, 8, 15, 22, 29, and 36 (repeated every day) Carbamazepine 200-600 mg (second line therapy)	A potential candidate as a protective agent against oxaliplatin-induced neurotoxicity binding to the receptor sites associated with the activation of voltage-sensitive sodium channels	[37]
Alpha-Lipoic Acid	Oxaliplatin 130 mg/m² Raltitrexed 3 mg/m² every 3 weeks Alpha-lipoic acid 600 mg i.v. once a week for 3 to 5 weeks 600 mg three times a day orally	Able to counteract cumulative oxaliplatin-related peripheral sensory neuropathy in Colorectal cancer	[41]
Amifostine	Raltitrexed 3 mg/m² oxaliplatin 130 mg/m² every three weeks (9 patients) Irinotecan 175 mg/m² oxaliplatin 85 mg/m² both given i.v. on days 1 and 14 every four weeks Amifostine 500 mg intravenous	Protection of peripheral nerves from the toxicity of alkylating agents No compromise in the antitumor activity of therapy in Advanced colorectal cancer	[38]

experiencing full relief of acute neurotoxicity during subsequent cycles of therapy has been significantly higher in the venlafaxine group (31% vs. 5%). Furthermore, at three months post-treatment, at a time when no patient remained on oxaliplatin therapy, a significantly higher number of patients in the venlafaxine arm had no neurotoxicity (39% vs. 6%), and significantly fewer have had grade 3 neurotoxicity (0 vs. 33%).

Wang WS et al[32] have demonstrated that a lower percentage of grade 1-2 peripheral neuropathy has been obtained by glutamine addiction compared to standard therapy (16.7% vs. 38.6%) after two cycles of treatment, and a significantly lower incidence of grade 3-4 neuropathy after four (4.8% versus 18.2%) and six cycles (11.9% vs. 31.8%).

Attempts to improve the tolerability of oxaliplatin have been done through the combined use of Neurotropin. Benefits from this association have been shown by trials enrolled patients with grade 2-3 neurotoxicity randomly divided into two groups, one of which received neurotropin treatment: significantly results have been reported in the neurotropin group[33]. Other drugs, including Glutathione[37], carbamazepine[38], Amifostine[39], have been also successfully tested.

It is reported that several "natural medicines" like as curcumin[40], ginkgo biloba[41], alpha-lipoic acid[42] and the Kampo medicine, Goshajinkigan[34], has been considered effective neuro-protective agents, without adverse effects.

Taken together and given the lack of confirmatory evidence that these pharmacologic agents interfere with antitumor efficacy, it is reasonable to consider them, at least in patients being treated with oxaliplatin. Until further information is available, we would not pursue this approach in the adjuvant setting. Accrual to a confirmatory randomized, placebo-controlled trial in patients receiving adjuvant therapy for colon cancer has been completed by the North Central Cancer Treatment Group (NCCTC, NCT00316914), which should settle the question of whether this therapy is worthwhile and safe in the adjuvant setting.

While these data seem promising, confirmation in larger trials is needed. Noticeable, the potential pitfalls of relying upon phase II studies to guide practice, can be illustrated by the experience with xaliproden, a neurotrophic agent that showed promise in small phase II studies. A phase III trial has been conducted in which 649 patients have been randomly assigned to xaliproden or placebo in conjunction with oxaliplatin-based chemotherapy. In a preliminary report presented in 2006, there has been a lower incidence of grade 3 sensory neuropathy with xaliproden (17% vs. 11% with placebo). However, the overall incidence of neurotoxicity was the same (73% on both arms), there was no increase in the total cumulative dose of oxaliplatin, or in the time patients could remain on treatment, or the percentage of patients with complete recovery after treatment with oxaliplatin (49% vs. 47%). Thus, there appeared to be no clinically meaningful benefit from the use of xaliproden[43].

CONCLUSIONS AND FUTURE OUTLOOK

Strategies previously described allowing physicians to improve the efficacy of cancer therapy. On the other hand, the clinical utility of the described strategies in Oxaliplatin based-therapy is in part limited by the evidence that natural remedies improve clinical outcomes is still an open question. The cost-effectiveness of these procedures is unknown.

Results from several strategic approaches optimized for management of oxaliplatin-induced neuropathy seem promising, but confirmation in larger trials is still needed.

Many of natural protective substances against toxicity of oxaliplatin are antioxidants. There are some of these that have been studied by several authors such as calcium and magnesium or Guilongtongluofang. An italian working group has demonstrated that the repetitive administration of antioxidants silibinin (the principal component of the silymarin complex) and -tocopherol reduced oxaliplatin-dependent pain[44].

Over the next few years, it is fundamental that pharmaceutical companies develop extensive trials on the standardization strategies suitable for routine clinical application in Oxaliplatin therapy.

In summary, with the increasing number of novel validated Oxaliplatin based schedules, oncologists will have new means to make treatment decisions, as well as correlation between nutrition and cancer[45,46], and may eventually be personalized on the patients in order to minimize toxicity[47].

Based on these purposes, the clinician and the pharmacists may join together to estimate advantages and restriction, in terms of costs and applicability, of the most suitable strategies to scheduling in oxaliplatin based therapy.

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