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Postoperative Exacerbation of Oxaliplatin-induced Neurotoxicity in Gastrointestinal Cancers: A Case Series

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Abstract. *Background/Aim: Oxaliplatin-induced neurotoxicity (OIN) can be severe and dose-limiting with clinically significant symptoms that persist for years. Few published reports have described postoperative exacerbation of OIN and more longitudinal data are needed to better characterize the phenomenon. Patients and Methods: We identified 13 patients diagnosed with colon (n=7), rectal (n=4) or pancreatic (n=2) cancer who experienced postoperative OIN exacerbation at our medical center. Charts were reviewed for demographic and clinical data regarding OIN. Results: OIN exacerbation was documented 0.5-7.0 months after the first surgery following oxaliplatin exposure, with a median duration of 10.6 months (range=1.4-86.1 months). OIN exacerbation persisted in 3/13 patients at last follow-up, and improved to pre-operative levels in 6/13 patients (with complete resolution in 4/13) within a median of 3.6 months from initial exacerbation. Conclusion: Given the widespread use of oxaliplatin in neoadjuvant and first-line treatment for gastrointestinal cancers, further study is warranted to prospectively and systematically define risks for postoperative OIN exacerbation.*

Oxaliplatin is used to treat colorectal cancer and other gastrointestinal malignancies in the neoadjuvant, adjuvant, and metastatic settings (1-6). One of its predominant and often dose-limiting toxicities is peripheral sensory neuropathy. Acute oxaliplatin-induced neurotoxicity (OIN) manifests as paresthesias of the extremities and/or laryngopharynx and is typically associated with cold-induced dysesthesia (7-9). Chronic OIN is due to cumulative oxaliplatin dose and can result in permanent functional limitation, including impaired fine motor skills, changes in proprioception, increased fall risk, and pain. Unlike acute OIN, chronic OIN does not resolve between treatment cycles and may become permanent (10).

There is wide variation in the clinical course of OIN, but studies have consistently shown almost all patients will experience at least mild acute neuropathy starting with the first treatment cycle (1, 11, 12). Dose-limiting oxaliplatin-induced sensory neuropathy occurs at cumulative doses between 667-810 mg/m^2 (7-9 cycles) (10, 13, 14). Though risk estimates vary considerably, incidence of severe (Common Terminology Criteria for Adverse Events (CTCAE) Grade 3+) chronic neuropathy may be up to 50% depending on treatment duration (15). Hyper-acute peripheral neuropathy, defined as upper extremity and laryngopharyngeal dysesthesia within 24 hours of the first cycle of chemotherapy, may be one clinical predictor of persistent OIN (16). Other associated factors include duration and intensity of symptoms after six treatment cycles, body surface area (BSA), and concomitant use of bevacizumab, while factors such as age, sex, performance status, comorbid diabetes, and prior treatment history do not seem to be associated (17, 18). Although one longitudinal study found no clinically significant increase in neurotoxicity relative to baseline after a seven-year follow up period, multiple others have documented persistence of chronic OIN for years after treatment (19-21).

Recent data from the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) study, designed to explore non-inferiority of shorter adjuvant treatment (3 *vs.* 6 months) with leucovorin, fluorouracil, and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CapeOX) in stage III colon cancer, further support the association between cumulative oxaliplatin dose and OIN (22). In this analysis of six

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Table I. *Patient characteristics*.

Patient ID	Gender	Age[1]	Race	Ethnicity	Primary cancer	Tumor location	Tumor differentiation[2]	AJCC stage
1	M	33	White	Non-Hispanic	Colon	Sigmoid colon	Moderately differentiated	ypT2N1bM1
2	F	46	White	Non-Hispanic	Colon	Sigmoid colon	Well differentiated	TxNxM1[3]
3	M	53	Other	Hispanic	Colon	Descending/sigmoid colon	Moderately differentiated	ypT3N0M1
4	F	58	American Indian/ Alaska Native	Hispanic	Colon	Sigmoid colon	Moderately differentiated	pT4aN1aM0
5	F	47	White	Non-Hispanic	Colon	Distal sigmoid colon	Moderately differentiated	pT3N1aM0
6	F	50	White	Non-Hispanic	Colon	Sigmoid colon	Moderately differentiated	pT4aN0M0
7	M	41	Black	Non-Hispanic	Colon	Sigmoid colon	Poorly differentiated	pT3N0M1
8	F	61	White	Non-Hispanic	Rectal	Distal rectum	Poorly differentiated	pT2N0M0
9	M	47	White	Non-Hispanic	Rectal	Distal rectum	Well differentiated	ypT2N0M0
10	M	46	White	Non-Hispanic	Rectal	Rectosigmoid junction	Well-moderately differentiated	T3aN1M1
11	M	51	White	Hispanic	Rectal	Distal rectum	Moderately differentiated	uT2N1M0
12	M	57	Other	Non-Hispanic	Pancreatic	Pancreatic head	Well differentiated	ypT3N1M0
13	F	60	White	Non-Hispanic	Pancreatic	Pancreatic head	Moderately-poorly differentiated	ypT3N1M0

[1]At diagnosis; [2]All cancers are adenocarcinoma; [3]No stage documented, extensive metastatic disease present at diagnosis. AJCC: American Joint Committee on Cancer.

randomized phase 3 trials encompassing 12,834 patients, neuropathy was the most common indication for dose reduction. Further, significantly less grade 3-4 peripheral sensory neuropathy was reported in the three-month treatment arm compared to the six-month treatment arm. In a sub-analysis from one study group, this discrepancy was found to persist for the entire seven-year study period.

In light of these findings, it is important to characterize the clinical patterns of OIN and understand factors that may impact its duration and severity (11). One hypothesis is that anesthesia exposure leads to OIN exacerbation. While the mechanism is not completely understood, it has been proposed that OIN exacerbation may be related to a redistribution of intra-erythrocytic oxaliplatin metabolites in the setting of perioperative hemolysis (23). This is supported by the finding that cumulative OIN may correlate with intra-erythrocytic drug concentration, as oxaliplatin accumulates within erythrocytes more so than other platinum agents (10, 24).

One prospective case series of patients with primary colon or adrenal tumors who received neoadjuvant oxaliplatin-containing regimens showed postoperative OIN exacerbation in seven of 12 patients (23). Another report described three patients with metastatic colorectal cancer who experienced mild transient neurotoxicity after initial treatment with an oxaliplatin-containing regimen and later reported exacerbation or functional impairment within two weeks after resection of metastases, with symptoms persisting up to one year following surgery (25). One patient with hepatocellular carcinoma who received neoadjuvant sorafenib, gemcitabine, and oxaliplatin described escalation from CTCAE Grade 1 to Grade 2 neurotoxicity following liver resection, which persisted and ultimately led to oxaliplatin discontinuation (26).

Given the large number of patients with gastrointestinal cancers who are treated with platinum-based regimens in the perioperative setting, understanding the relationship between surgery and OIN exacerbation is important. Specifically for locally advanced rectal cancer, total neoadjuvant therapy with FOLFOX has been added to the National Comprehensive Cancer Network (NCCN) Guidelines and has been adopted as a standard practice (27, 28). Among patients with borderline resectable pancreatic cancer, neoadjuvant therapy with oxaliplatin-containing chemotherapy regimens is leading to improved surgical outcomes (29-31). Data also suggest improvement in outcomes with neoadjuvant oxaliplatin-containing therapy in adenocarcinoma of the stomach and esophagogastric junction (32).

In this case series, we aim to describe and better characterize postoperative OIN exacerbation in patients with cancers of the colon, rectum, or pancreas.

Patients and Methods

We identified adult patients with primary gastrointestinal cancers who received neoadjuvant oxaliplatin and experienced new or exacerbated postoperative OIN through provider recall. Patients were treated between 2010-2017 in the Gastrointestinal Oncology Clinic at the University of California San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center. All patients received at least one dose of oxaliplatin prior to undergoing a surgical procedure. A structured retrospective chart review was generated following approval by the UCSF Institutional Review Board (study #17-21995).

Past medical history of each patient was reviewed to assess for conditions that could predispose to neuropathy (*e.g.*, diabetes). Cumulative total oxaliplatin was calculated based on the patient's

Table II. *Oxaliplatin treatment regimens.*

Patient ID	Time to OX (mo)[1]	Prior regimens	OX regimens	OX cycles[2]	OX dose & schedule (mg/m^2)	OX dose reductions; Indication	Cumulative OX dose (mg/m^2)	Treatment duration (mo)
1	0.7	-	FOLFOX+Cetux	6	85 Q2W	No	536	2.6
2	0.5	-	FOLFOX+Bev	10	85 Q2W	30% beginning C9; neuropathy	820	4.6
3	0.7	-	CapeOX+Bev	10	130 Q3W	No	1300	6.4
4	13.3	-	CapeOX+Bev	8	97.5 Q3W	25% beginning C1; patient preference	776	4.9
5	13.7	FOLFIRI	FOLFOXIRI+Bev	6	85 Q2W	No	502	2.8
6	1.4	-	FOLFOX	9	85 Q2W	20% beginning C9; thrombocytopenia	766	3.7
7	1.2	-	CapeOX	2	130 Q3W	No	428	0.6
			FOLFOX	2	85 Q2W			0.5
8	4.2	F+XRT	FOLFOX	4	85 Q2W	% unknown beginning C3; neutropenia	3413	2.1
9	3.6	F+XRT	FOLFOX	6	85 Q2W	No	687	2.4
			FOLFOX	2	85 Q2W			0.4
10	0.9	-	FOLFOX	10	85 Q2W	No	1228	6.2
			CapeOX	3	130 Q3W			1.4
11	4.2	Cape+XRT	FOLFOX	8	85 Q2W	No	664	4.1
12	1.8	-	FOLFIRINOX	18	85 Q2W	No	1523	9.0
13	1.9	-	FOLFIRINOX	12	85 Q2W	20% beginning C8; thrombocytopenia	891	6.8
Median	1.6			7			766	4.1
Range	0.5-13.7			2-18			341-1523	1.1-9.0

[1]Relative to date of diagnosis; [2]Total number of cycles; [3]Cumulative dose estimated based on starting regimen dose. OX: oxaliplatin; FOLFOX: 5-fluorouracil, folinic acid, and oxaliplatin; Cetux: cetuximab; Bev: bevacizumab; CapeOX: capecitabine and oxaliplatin; FOLFIRI: 5-fluorouracil, folinic acid, and irinotecan; FOLFOXIRI: 5-fluorouracil, folinic acid, oxaliplatin and irinotecan; F+XRT: 5- fluorouracil and radiation therapy; Cape+XRT: capecitabine and radiation therapy; FOLFIRINOX: 5-fluorouracil, folinic acid, irinotecan and oxaliplatin.

BSA (using height and weight recorded immediately prior to treatment initiation), dose in milligrams (mg), and number of treatment cycles, adjusting for dose reductions as appropriate. Data on neuropathy was abstracted from review of clinic notes. OIN exacerbation was defined as worsened neuropathy (numbness, tingling, pain, and/or temperature sensitivity) from baseline, as described by providers based on qualitative patient report. Resolution of OIN exacerbation was assessed in the same manner.

Results

Demographic and clinical characteristics of the patients are summarized in Table I. Median age at diagnosis was 50 years (range=33-61 years). None of the 13 patients reported any signs or symptoms of neuropathy, nor comorbid conditions predisposing to neuropathy, prior to initiating chemotherapy with oxaliplatin. Seven patients were treated for colon adenocarcinoma, four for rectal adenocarcinoma, and two for pancreatic adenocarcinoma. The demographic characteristics were representative of patients seen in the Gastrointestinal Oncology practice at our institution (54% male and 62% non-Hispanic white).

Oxaliplatin was administered as a component of first- or second-line chemotherapy to all patients. Table II presents additional information regarding each individual regimen. In colon cancer patients (n=7), oxaliplatin was administered before primary tumor resection in two cases, with the remaining five receiving oxaliplatin prior to resection of metastases. All rectal cancer patients (n=4) and pancreatic cancer patients (n=2) received oxaliplatin before resection of the primary tumor. Median total cumulative oxaliplatin dose was 766 mg/m^2 (range=341-1523 mg/m^2) administered over a median period of 4.1 months (range=1.1-9.0 months), corresponding to a median of 7 treatment cycles (range=2-18 cycles). Of the 13 patients, five received dose reduction of oxaliplatin due to neuropathy and/or cytopenia. Almost all (12/13) patients developed stable or progressive OIN during the course of their treatment, while one developed neuropathy after completion of oxaliplatin and a subsequent surgery. There was an average interval of 3.9 months (range=0.3-25.8 months) between the final oxaliplatin dose and surgery. Total duration of symptoms varied, but 12/13 patients had reported improvement in neuropathy prior to surgery. While all 13 patients developed OIN exacerbations after surgery, 7/13

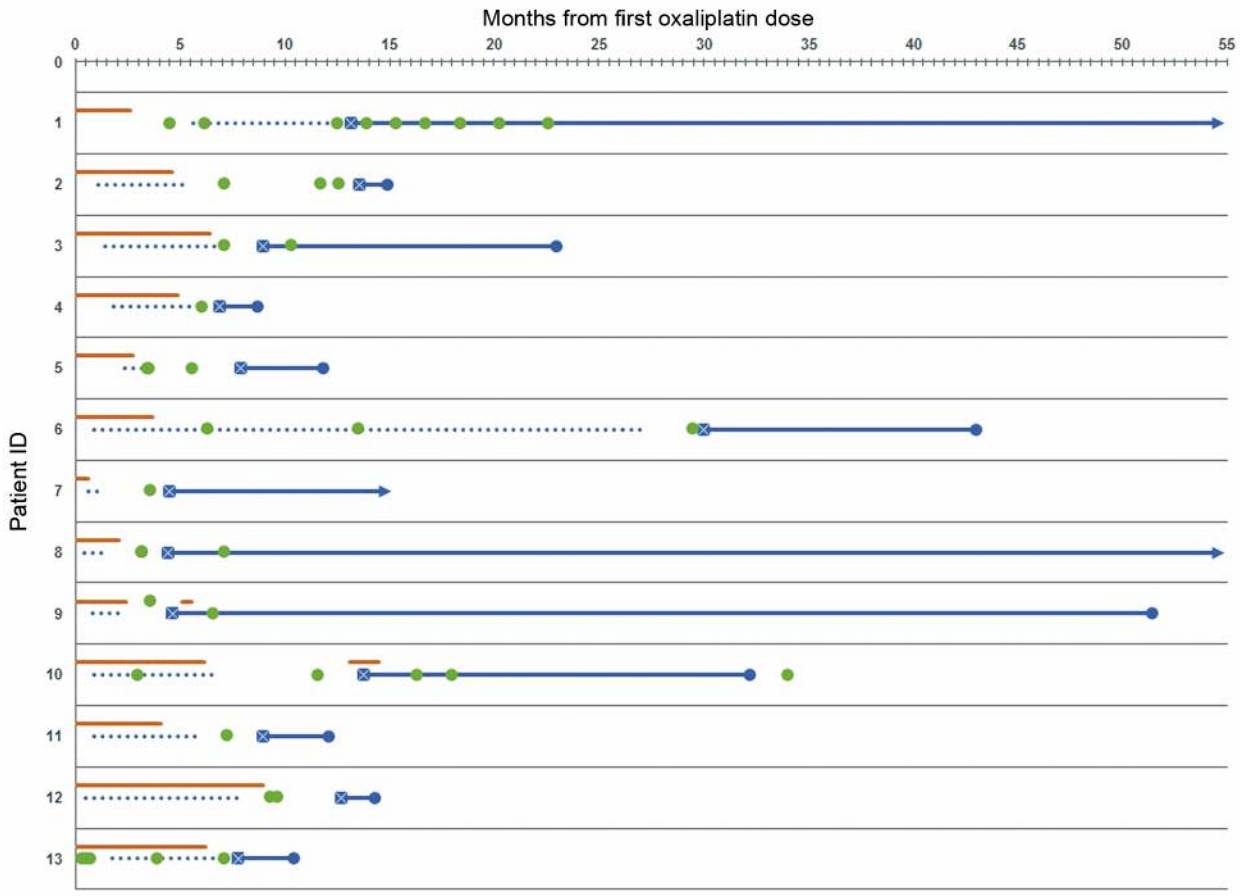

Figure 1. *Time course of oxaliplatin-induced neuropathy development and exacerbation (in months) for each patient, normalized to the time of first oxaliplatin dose. Oxaliplatin treatment duration is presented by orange lines. Surgical events are presented by green dots. Neuropathy is presented by blue lines (arrows indicate ongoing neuropathy at time of last follow-up), dotted when experienced prior to the first documented report of exacerbation (blue box).*

patients underwent multiple procedures under anesthesia prior to OIN exacerbation. Figure 1 shows the clinical time course of neuropathy relative to procedures performed under anesthesia for each patient, normalized relative to first oxaliplatin dose.

The median follow-up time was 10.7 months from the date of OIN exacerbation. Significant variation in the course and severity of OIN exacerbation was observed. OIN exacerbation was first documented between 0.5 and 7.0 months after surgery, with a median duration of 10.6 months (range=1.4 to >86.1 months). At the time of last follow-up, 23% (3/13) of patients reported ongoing OIN exacerbations. OIN improved to pre-operative levels in 46% (6/13) of patients, with complete resolution in 31% (4/13). For patients with localizing details recorded, predominant sites of neuropathy included feet/soles (42%, 5/12), bilateral distal upper/lower extremities (42%, 5/12), and hands/fingertips (16%, 2/12). Formal neuropathy grade was not routinely documented in the medical record. While patients described intense discomfort with symptom flares, no severe functional limitations or falls were documented.

Discussion

The use of oxaliplatin in the neoadjuvant setting is increasingly common in clinical practice (30, 31). As such, understanding the effects of anesthesia exposure on OIN is of particular importance, especially given the possible functional implications of chronic toxicity. In this case series, we present a group of 13 patients who reported aggravation of pre-existing OIN following anesthesia exposure. The variability in demographics, cancer characteristics and oxaliplatin dosing that we report suggests postoperative OIN exacerbation has the potential to affect a broad set of patients who receive oxaliplatin in the neoadjuvant setting.

Options for treatment of OIN are limited, making it difficult to control exacerbations of symptoms following surgery. Acupuncture has been anecdotally shown to be effective for neuropathy caused by other chemotherapies, but this has not been studied extensively (33, 34). Despite conflicting results from small retrospective studies, calcium and magnesium infusions have been shown, in a phase III randomized study, to have no significant effect in reducing OIN (35, 36). While duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI), has been shown to be effective in reducing pain for patients with painful chemotherapy-induced neuropathy, its effect in non-painful neuropathy is not well characterized (37). More broadly, pharmacotherapies traditionally used for neuropathy, such as gabapentin, have not performed well in randomized trials in the setting of chemotherapy-induced symptoms (38). Given the dearth of treatment options, management of cancer patients whose neuropathy worsens postoperatively is challenging. As such, there is a need to better understand this clinical entity to enable providers to identify those at high risk for exacerbation of OIN and to better counsel patients on the possible risks of anesthesia exposure.

To our knowledge, this is the largest case series describing postoperative OIN exacerbation. Several limitations of this exploratory study, and opportunities for prospective investigation, should be acknowledged. Given the retrospective nature of the study, we were unable to ascertain the specific duration of anesthesia exposure. We do demonstrate a temporal association between surgery and OIN exacerbation, however, the question of whether there is a dose-response relationship between anesthetic exposure and OIN severity warrants future prospective studies. The retrospective nature of the study also precluded correlative laboratory or radiographic measurements. For example, one previous study reporting OIN exacerbation examined intraerythrocytic and unbound plasma oxaliplatin levels in the pre- and post-operative settings, as well as unconjugated bilirubin. Another showed evidence of redistribution of oxaliplatin metabolites from erythrocytes to plasma (23). Finally, recent evidence suggests an association between psoas muscle cross-sectional area, a marker of nutritional status, and risk of OIN (39). While we did not have these data in our patient cohort, future studies should examine putative biomarkers for OIN. Finally, recall bias is a possibility in a retrospective study such as ours, though structured chart review was completed to identify any mention of OIN severity in the medical record. Future prospective study of postoperative OIN exacerbation will require regular check-ins (possibly using digital health technology) to pinpoint the onset and resolution of OIN and administration of validated questionnaires to score symptom severity including impact on activities of daily living and quality of life (21, 40).

Conclusion

Postoperative OIN exacerbation is experienced by a diverse group of gastrointestinal cancer patients. Our data suggest this phenomenon warrants future study. Future studies should aim to identify prospective biomarkers for exacerbation to determine which patients are at highest risk and to provide perioperative patient counseling.

Conflicts of Interest

The Authors disclose no conflicts of interest pertaining to this manuscript.

Authors' Contributions

AG: Conceived and designed the analysis, collected data, performed analysis, contributed to manuscript; EW: Conceived and designed the analysis, collected data, performed analysis, contributed to manuscript; KVL: Contributed data, contributed to manuscript; PC: Conceived and designed the analysis, contributed data, contributed to manuscript; CA: Conceived and designed the analysis, contributed data, contributed to manuscript.

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