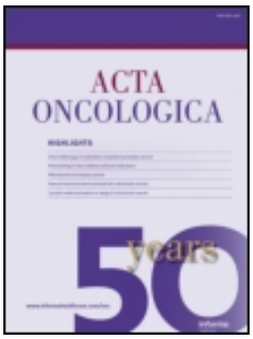

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LETTER TO THE EDITOR

An association between transient hypokalemia and severe acute oxaliplatin-related toxicity predominantly in women

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To the Editor

Oxaliplatin is a third generation platinum compound frequently used in the treatment of colorectal cancer [1]. Besides myelosuppression, peripheral neuropathy is a well recognized toxicity frequently limiting its use [2]. We report a single-institution prospective experience with regards to severe acute oxaliplatin-related toxicity, and highlight an unexpectedly high incidence of transient hypokalemia in these patients, predominantly in women.

The possible mechanisms of oxaliplatin-related neuropathy remain unclear. Multiple mechanisms of actions have been proposed including the use of various neuroprotective agents in hope of achieving adequate oxaliplatin doses with less neuropathy [3]. Most studies have looked mainly into chronic sensory neuropathy such as numbness. Much less is known about acute reactions such as laryngopharyngodysthesias or anaphylaxis. We performed a prospective analysis of our patients who had oxaliplatin exposure and selected those who developed acute oxaliplatin reactions requiring hospitalizations and summarized pertinent information on those who met our inclusion criteria.

We prospectively collected data on acute oxaliplatin-related reactions at our institution between January 2008 and June 2009. During this duration, a total of 772 patients (452 males and 320 females) were exposed to oxaliplatin-related chemotherapy. All the patients were receiving oxaliplatin either as a cyclical or weekly regime.

Oxaliplatin-related reactions commonly reported included breathlessness, numbness, voice hoarseness and anaphylaxis. Severe oxaliplatin-related reactions were defined as those reactions requiring hospitalization. Baseline laboratory tests, including urea, creatinine and electrolytes are routine at our institution before each cycle of chemotherapy. Patients were allowed to proceed with chemotherapy only if electrolytes were within normal range (sodium 135–145 mmol/L and potassium 3.5–4.5 mmol/L). Patients who had prior oxaliplatin exposure during this period and who developed severe oxaliplatin reactions requiring inpatient admissions were identified into our study.

Eleven of 772 patients (1.5%) were identified with such reactions (Table I). Information pertinent to this study group was summarized in Table I. There was a female predominance with seven women and four men within the group and ages ranged from 36 to 75 years old. All patients had a good performance status. Two of these 11 patients required mechanical ventilation in an intensive care setting. There were no recorded deaths.

Nine of 11 patients who developed severe reactions to oxaliplatin had laboratory investigations done immediately post reaction. The remaining two patients were relatively well and admitted for overnight observation without laboratory testing. We noted a high incidence of hypokalemia in seven of nine patients (78%). It was further noted that six of these seven hypokalemic individuals were female, and the remaining two who did not display hypokalemia were male. Transient hypokalemia appeared to occur with the rapid onset of oxaliplatin adverse drug reactions. In all but one hypokalemic patient, intravenous potassium infusion was commenced with improvement in the clinical syndrome noted over several hours, although a recovery that was spontaneous or due to other supportive measures instituted cannot be excluded. There was

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Table I. Details of patients who experienced severe oxaliplatin-related reactions.

	Age/Sex	Chemotherapy Regime	Cumulative Oxaliplatin Dose/(mg)	Clinical reaction and management	Baseline laboratory results (mmol/L)	Post reaction laboratory results (mmol/L)	
					K^+	K^+	Ca^{2+}
1	M/58	XELOX	200	Breathlessness	4.0	4.3	2.17
2	F/36	Oxaliplatin/ Cetuximab	350	Anaphylaxis requiring intubation	4.5	3.1	2.23
3	F/65	Cetuximab/ XELOX	2110	Anaphylaxis requiring intubation	3.5	3.0	2.03
4	F/47	XELOX	430	Breathlessness	3.5	2.5	2.12
5	F/60	XELOX	300	Breathlessness and rhonchi; salbutamol nebulization	3.6	2.3	2.31
6	M/57	XELOX	150	Breathlessness and stridor; salbutamol nebulization	3.7	3.0	2.28
7	F/70	XELOX	1750	Giddiness, breathlessness and numbness	3.7	2.7	ND
8	F/70	FOLFOX	390	Chest tighness at completion of infusion	3.1	3.1	ND
9	F/75	FOLFOX	60	Breathlessness with rhonchi; salbutamol nebulization	4.4	ND	ND
10	M/75	FOLFOX	240	Chest tightness and facial flushing	4.4	3.8	ND
11	M/70	XELOX	960	Flushing, hoarseness of voice, wheezing, difficulty swallowing	4.1	ND	ND

ND: not done.

an evident, but non-significant predominance of women who developed severe acute oxaliplatin-related toxicity (odds ratio 2.5, Fisher's test $p=0.22$).

Other possible causes which may contribute to hypokalemia at the time of reaction were considered. One patient was on frusemide at the time of drug reaction (Patient 1). There was no documented history suggestive of gastrointestinal losses. Nebulised salbutamol, a beta-agonist, was used in the acute management of the oxaliplatin-related reaction in three of the 11 patients, all of whom had hypokalemia (Patient 5, 6 and 9).

Discussion

Acute oxaliplatin neuropathy is common and occurs within minutes of infusion, frequently presenting as parasthesia [4]. Severe cases include laryngopharyngodysthesia with airway compromise. While the mechanism of oxaliplatin-related neuropathy remains uncertain, electromyography (EMG) studies have demonstrated peripheral motor nerve hyperexcitability coinciding with symptoms of acute neuropathy [5]. Present data suggest that acute oxaliplatin-induced neuropathic symptoms are due to prolonged activation of voltage-gated sodium channels from rapid chelation of calcium by oxaliplatin-induced oxalate, leading to a hyperexcitable state [6].

Transient hypokalemia appeared to occur with the rapid onset of oxaliplatin adverse drug reactions in our study. Other possible causes of hypokalemia (gastrointestinal losses or medication-related) were excluded. Acute respiratory alkalosis (hyperventilation) has been reported to result in a clinically significant increase in plasma potassium levels with a resultant post-hyperventilation ventilation-rate dependent hypokalemic overshoot on recovery. However, in our study patients, levels of serum bicarbonate remained similar both before and after chemotherapy suggesting that ventilation-related alkalosis was unlikely [7]. Calcium and magnesium infusions were not used in our patients and it is unclear if they would have had any protective effects.

Recently reported *ex-vivo* work suggests that oxaliplatin may interfere with voltage-gated potassium channels [8]. We hypothesize that axonal membrane hyperpolarization [9,10] may account for the observed hypokalemia, with potassium ion channel activation resulting in an intracellular influx of potassium. This resulted in tetany, numbness and breathlessness which is seen in oxaliplatin reactions. The differing potassium levels across the cell membrane eventually equilibrate, restoring transmembrane potential. Hence, such acute reactions tend to be transient.

There was an evident, but non-significant predominance of women who developed severe acute oxaliplatin-related toxicity (odds ratio 2.5, Fisher's test $p=0.22$). Based on our series, females appeared more prone to severe oxaliplatin reactions for which the reason remains unclear, and all females manifested acute hypokalemia. We can draw possible

parallels with the incidence of acute neurological toxicity related to the use of metoclopramide which occurs more commonly in females [11].

Although oxaliplatin has been in widespread use, the mechanisms underlying acute oxaliplatin-related toxicity remain uncertain. Our observation of a high incidence of transient hypokalemia during severe acute oxaliplatin-related reactions, together with a characteristic syndrome, suggests a possible involvement of potassium ion channels in severe acute oxaliplatin-related toxicity. From a clinical and biologic viewpoint, further investigation is warranted, particularly into the use of prophylactic potassium infusion as a method to avoid acute oxaliplatin-related toxicity.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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