Journal on Oncology

www.journalononcology.org

Case Report

Open Access, Volume 3

Monocular Tunnel Vision Produced by Oxaliplatin

Guido V Schiappacasse[1,2,3]*

[1]Chief Physician of the Oncology Department, Clinical Hospital of Viña del Mar, Limache Street 1741, Viña del Mar, Chile.

[2]Oncology Department, Ciudad del Mar Clinic, Libertad Avenue 1159, Viña del Mar, Chile.

[3]Oncology Department, Bupa Reñaca Clinic, Anabaena Street 336, Viña del Mar, Chile.

Abstract

This case report presents a 60-year-old male with metastatic colon cancer. After the first administration of FOLFOX6 plus bevacizumab, the patient presented sudden, transient and repetitive monocular tunnel vision. The clinical and complementary study allows the diagnosis of retrobulbar optic neuritis caused by oxaliplatin. This complication by oxaliplatin is rare, therefore, this report contributes to the scarce literature on the subject. Finally, we conclude that ocular disorders should be looked for in a targeted manner when using oxaliplatin, because if the patient's exposure to this cytotoxic drug continues, ocular damage may be irreversible.

Keywords: Colon cancer; FOLFOX; Optic neuritis; Oxaliplatin; Tunnel vision.

Abbreviations: DACH: 1,2 diaminocyclohexane; DNA: Deoxyribonucleic Acid; RNA: Ribonucleic Acid; Mg: milligram; M2: square meter; ST: Segment of the Electrocardiogram. This represents the isoelectric period when the ventricles are between depolarization and repolarization; Her2/neu: Human epidermal growth factor receptor 2; K-Ras: a part of the RAS/MAPK pathway. The protein relays signals from outside the cell to the cell's nucleus.; N-Ras: Protein encoded by the neuroblastoma RAS viral oncogene homologue. This is a part of the RAS/MAPK pathway; B-Raf: Serine/threonine-protein kinase. This is a part of the RAS/MAPK pathway.; ECOG: Scale designed by the Eastern Cooperative Oncology Group (ECOG) to assess the quality of life of cancer patients; SPECT: Single photon emission computed tomography.; FOLFOX6: chemotherapy regimen containing 5-fluorouracil and oxaliplatin; BCVA: The best corrected visual acuity; OCT: Macular and optic nerve optical coherence tomography; HIV: Human Immunodeficiency Virus; FOLFIRI: Chemotherapy regimen containing 5-fluorouracil and irinotecan.

Introduction

In 1,964, an alternating electric field was experimentally applied by means of platinum electrodes through a chamber where Escherichia coli bacteria were growing. An inhibitory effect was observed on the cell division of this microorganism, but not on its cell growth. This resulted in the anomalous growth of filamentous bacteria up to 300 times the normal length. This effect was due to the formation by electrolysis of a small proportion of compounds containing inorganic platinum in the presence of chlorine and ammonium ions (approximately 1 to 10 parts per million) [1]. Later, it was determined that the cis form of the diamino complex was responsible for the inhibition of Escherichia coli cell division [2]. Subsequently, sarcoma tumor 180 was transplanted into Swiss white mice and then these were exposed intravenously to cisplatin (cis-dichlorodiaminoplatin II). Regression of the implanted tumor was seen in 100% of the mice. Thus, the first evidence of the antitu-

Manuscript Information: *Received: Jun 12, 2023; Accepted: Jul 06, 2023; Published: Jul 13, 2023*

Correspondance: *Guido V Schiappacasse, Chief physician of the Oncology Department, Clinical Hospital of Viña del Mar, Limache Street 1741, Viña del Mar, Chile. Tel: +56959021201; Email: g.schiapp@hotmail.com*

Citation: *Schiappacasse GV. Monocular Tunnel Vision Produced by Oxaliplatin. J Oncology. 2023; 3(2): 1094.*

mor effect of cisplatin was obtained [3]. Following the discovery of the first platinum with antineoplastic action, thousands of platinum compounds have been screened for the chemicals with the highest antitumor activity and clinical efficacy.

Along this path, we now know oxaliplatin (oxalate (trans-L-1,2-diaminocyclohexane) platinum), which is a third-generation platinum antitumor analog in which the 1,2-diaminocyclohexane (DACH) ligand substitutes for the amino group of cisplatin [4]. This agent is very useful in clinical oncology and is frequently applied together with fluoropyridines as an adjuvant in gastric [5,6], pancreatic [7] and colorectal cancer [8-10], in perioperative gastric cancer [11], as a neoadjuvant in rectal cancer [12]; and in advanced stage in gastric [13], pancreatic [14] and colorectal cancer [15]. As a result of its frequent use in digestive cancers, it is very important that medical oncologists know how to handle this drug with expertise.

The cytotoxic effects of oxaliplatin are due to the fact that this drug triggers the apoptosis process in the tumor cell due to DNA chain damage in the neoplastic cell, inhibition of DNA and RNA synthesis and immunological effects. Oxaliplatin also shows synergistic effect with other cytotoxic drugs [16].

However, adverse reactions to oxaliplatin result in restricting the dose of administration and reduce the therapeutic index of the drug. The most frequent adverse effects are:

a) Hematopoietic: Oxaliplatin is moderately myelotoxic and the severity of this toxicity is dose-dependent, generally between 85 and 135 mg/m^2 [16]. Severe neutropenia is frequent, but febrile neutropenia is described in only 4% of cases [17]. In contrast, anemia and thrombopenia are mild to moderate [16]. Autoimmune anemia and thrombopenia due to hypersensitivity to repeated administrations of oxaliplatin have also been described [18].

b) Gastrointestinal: Oxaliplatin affects the cells of the gastrointestinal tract since they have a high mitotic index. As a consequence, nausea, vomiting and diarrhea are described [19]. These adverse effects are usually mild to moderate.

c) Neuropathic: Oxaliplatin very frequently affects peripheral nerves. Acute and chronic peripheral neuropathy, with different but overlapping etiopathogenesis, have been described.

1) Acute peripheral neuropathy is due to the rapid chelation of calcium by the action of the oxalate compound of oxaliplatin. In this way, neuronal voltage-dependent sodium channels related to calcium ions are affected. Thus, oxaliplatin produces a primary distal sensory, axonal, symmetrical neuropathy without involvement of motor fibers [20]. Clinically, it is characterized by paresthesia, dysesthesia or allodynia of the distal portion of the extremities, lips and oropharyngolaryngeal region. It usually gets triggered by cold and occurs during or shortly after oxaliplatin administration. It is a transient condition, and usually subsides within a few hours or days [16].

2) Chronic peripheral neuropathy is due to oxaliplatin resulting in atrophy of a neuronal subpopulation in the dorsal ganglion root in the spinal cord. It has been shown in rat models that this cell subpopulation is characterized by having larger neurons than other subpopulations as well as by expressing parvalbumin [21]. This complication is related to the accumulated dose of the drug. It occurs in relation to cumulative doses of oxaliplatin of around 800 mg/m^2 [22]. Clinically, it is characterized by a loss of thermoalgesic and proprioceptive sensitivity, rarely impacting motor fibers, and is irreversible in less than 5% of cases [16].

On the other hand, ocular involvement is extremely rare among the known complications of oxaliplatin. However, blurred vision, loss of vision, tunnel vision, and altered color vision have been described in association with oxaliplatin use [23]. Ophthalmologic pathology such as cataracts, retinal opacities, optic neuritis, and inflammatory diseases such as conjunctivitis, blepharitis, uveitis, keratitis, and iritis have also been reported in association with oxaliplatin use [24].

The purpose of this article is to present a clinical case characterized by tunnel vision associated with initial exposure to oxaliplatin.

In this regard, we believe that this research contributes to enrich the literature on oxaliplatin-related eye disorders, with the ultimate goal of contributing to the better management of this drug commonly used in clinical oncology.

Case report

A 60-year-old male patient with a history of acute posteroinferior myocardial infarction with ST-segment elevation and hypertension treated with telmisartan (angiotensin II receptor blocker). The patient underwent coronary angiography and coronary stenting.

Six months later, the patient consulted due to a change in bowel habits. Complete colonoscopy showed an exophytic, friable, non-occlusive lesion of the sigmoid colon, with the rest of the large intestine and the distal ileum free of disease. The endoscopic biopsy was compatible with moderately differentiated tubular adenocarcinoma. The immunohistochemical study showed no microsatellite instability and HER2/neu was negative. In the polymerase chain reaction study, the K-Ras mutation in codon 12 was positive, while the mutations in N-Ras and B-Raf were negative. Chest, abdomen and pelvis scan showed several unresectable liver lesions.

The patient is in an adequate general state, eutrophic, well nourished, ECOG 1. General laboratory testing shows no alterations in blood cell counts, and liver and renal functions are preserved.

On cardiological study, the echocardiogram was normal (left ventricular ejection fraction of 62%). Cardiac SPECT with thallium/dipyridamole ruled out residual myocardial ischemia.

Therefore, the cardiologist authorized the initiation of first-line palliative chemotherapy with FOLOFX6 plus bevacizumab.

Within 24 hours of completing the administration of the first dose, the patient presented 6 episodes in 48 hours characterized by tunnel vision in the right eye. The left eye was not affected. This symptom was triggered by sudden changes in head position, had a rapid onset, lasting less than 30 seconds and with subsequent spontaneous recovery of vision. The symptomatology vanished after two days.

On ophthalmologic examination, the following stood out:

a) The best corrected visual acuity (BCVA) was 18/20 in the right eye and 20/20 in the left eye.

b) The Ishihara color test showed a mild protanopia (alteration of red color vision) in the right eye. Color vision was normal in the left eye.

c) Visual field examination was normal in both eyes.

d) Fundus examination did not show alteration of the retina or the optic nerve head. Thus, we ruled out retinal arterial vasospasm due to 5-fluorouracil [25] or retinal thrombosis due to bevacizumab [26] as the cause of this disease.

Specific ophthalmologic studies described the following:

a) The electrooculogram test in the right eye showed an alteration at the limit of normality with an Arden index of 1.60. In the left eye the result was normal, with an Arden index above 2.00 [27].

b) Macular and optic nerve optical coherence tomography (OCT) had a normal result. A normal OCT means that multiple sclerosis or neuromyelitis optic are less likely to be causes of this ocular disorder.

(c) The electroretinogram and evoked potentials had normal results.

c) Nuclear magnetic resonance study of the optic nerve and encephalic resonance were normal. This ruled out encephalic metastases or tumor compression of the optic nerve as the cause of the symptoms.

Etiological studies of the clinical picture showed the following:

a) Fasting glycemia levels and glucose tolerance test were within normal limits (ruling out metabolic neuropathy).

b) The patient has no history of alcoholism or tobacco use. Blood ethanol levels were negative (ruling out toxic neuropathy).

c) Plasma levels of vitamin B12 were within normal ranges (rules out a deficiency neuropathy).

d) The antibody studies were negative, thus eliminating the causal diagnosis of mesenchymal diseases and disease associated with antibodies against myelin oligodendrocyte protein.

e) Serology for Lyme disease, syphilis, toxoplasmosis, bartonellosis, toxocariasis, HIV, Epstein-Barr virus and cytomegalovirus were all negative. In addition, the tuberculin test was negative (ruling out infectious neuropathy).

After analyzing the patient's symptoms and signs, a diagnosis of right retrobulbar optic neuritis was made. On the other hand, considering the clinical history and laboratory tests, we can conclude that this ocular disease was caused by oxaliplatin exposure.

Therefore, oxaliplatin was suspended and second-line chemotherapy based on FOLFIRI and bevacizumab was started.

After 3 months of administration of the new therapy, the neoplasm remains stable and the patient has not presented ocular symptoms again. In addition, in the right eye, corrected visual acuity and color vision improved, and the Arden-index rose to 2.00.

Discussion

Ophthalmologic complications due to oxaliplatin are infrequent; however, some are recorded in the literature.

In this regard, in a Japanese retrospective study with n=55 cases treated with oxaliplatin, ocular disorders were described in 18.2% of the cases. Among them, blepharoptosis was described in 9.1%, visual field deterioration in 3.6%, reduction of visual acuity in 3.6%, ocular pain in 1.8%, ocular congestion in 1.8%, abnormal tearing in 1.8%, and blurred vision in 1.8%. These symptoms occurred during the initial period of treatment (during the first or second application of oxaliplatin), in all cases the symptoms were mild (grade 1 or 2), and in most cases there was observed spontaneous improvement [28].

In our clinical case, we concluded that the patient presented an acute right optic neuritis that was retrobulbar (because he did not present papilledema that shows alteration of the optic nerve head), mild, transient, and as a consequence of the use of oxaliplatin.

That said, the Naranjo algorithm evaluates the causality of adverse drug reactions [29]. If we apply it to our particular case, we obtain a score of 4, i.e., it is possible that oxaliplatin is the cause of the patient's optic neuritis (Table 1).

Table 1: Naranjo's algorithm applied to this clinical case.

Ask	Yes	Not	Does not apply	answer
Number 1	1	0	0	1
Number 2	2	-1	0	2
Number 3	1	0	0	1
Number 4	2	-1	0	0
Number 5	-1	2	0	-1
Number 6	1	0	0	0
Number 7	1	0	0	0
Number 8	1	0	0	0
Number 9	1	0	0	1

Ask 1: Are there conclusive previous reports about this adverse reaction?
Ask 2: Did the adverse reaction appear after the suspected drug was administered?
Ask 3: Did the adverse reaction improve when the prescribed drug was discontinued or when a specific antagonist was administered?
Ask 4: Did the adverse reaction recur when the prescribed drug was reintroduced?
Ask 5: Are there other causes (other than administration of the drug) that may themselves have caused the reaction?
Ask 6: Has the drug been detected in the blood (or other humors) in a toxic concentration?
Ask 7: Did the severity of the adverse reaction increase (decrease) when the dose of the prescribed drug was increased (decreased)?
Ask 8: Did the patient have a similar adverse reaction to the drug or their analogues at any exposure previous?
Ask 9: Was the adverse reaction confirmed by objective evidence?

On the other hand, we think that oxaliplatin-related optic neuritis should be considered as a special case of acute peripheral neuritis caused by oxaliplatin. This statement is based on our clinical case, where ocular symptoms had a rapid onset, toxicity was transient and symptoms disappeared after the treatment was discontinued. These clinical features are similar to those of classical acute peripheral neuropathy caused by oxaliplatin.

Despite the fact that oxaliplatin optic neuritis is rare, there are few reports in the literature [24,30-32]. In this regard, ophthalmologic pathology due to oxaliplatin is usually temporary and reversible. However, permanent changes, such as retinal damage and loss of visual fields, have occasionally been reported [24].

The pathologic mechanism of oxaliplatin ocular toxicity is not fully understood; however, damage to the retinal epithelium and the optic nerve are believed to cause this toxicity [24].

Finally, although oxaliplatin-related ophthalmologic pathology is usually transient and reversible, it should be kept in mind that late diagnosis and prolonged drug exposure can lead to irreversible sequelae in the optic nerve [33].

Conclusion

We can conclude that:

a) In every patient receiving oxaliplatin, a directed anamnesis and a general ophthalmologic examination should be performed to look for symptoms and signs of ocular toxicity caused by this drug.

b) If evidence of ophthalmologic toxicity due to oxaliplatin is found, the administration of the drug should be suspended immediately and the patient should be urgently referred to an ophthalmologist.

c) Although the diagnosis of optic neuritis is clinical, the complementary tests mentioned above are important to make a differential diagnosis.

d) If the diagnosis of optic neuritis caused by oxaliplatin is confirmed, the patient should not be re-exposed to the drug, because this increases the risk of irreversible damage to the optic nerve, with the consequent deterioration of the patient's quality of life.

e) This article is important because it contributes information to the scarce literature on the subject. In addition, this study attempts to address issues regarding the diagnosis and management of oxaliplatin-related optic neuritis.

We think that this is relevant for medical oncologists because oxaliplatin is widely used today.

Finally, since the subject of ocular toxicity caused by this drug is infrequent and not well known, it is relevant to acquire more knowledge on this subject.

Conflict of interest: The authors declare that they have no conflicts of interest.

References

1. Rosenberg B, Van Camp L, Krigas T. Inhibition of Cell Division in Escherichia coli by Electrolysis Products from a Platinum Electrode. Nature 1965; 205: 698–699.
2. Rosenberg B, Van Camp L, Grimley EB, Thomson AJ. The Inhibition of Growth or Cell Division in Escherichia coli by Different Ionic Species of Platinum (IV) Complexes. BJC 1967; 242(6): 1347-1352.
3. Rosenberg B, Van Camp L. The successful regression of large solid sarcoma 180 tumors by platinum compounds. Cancer Res. 1970; 30(6): 1799-802.
4. Faivre S, Chan D, Salinas R, Woynarowska B, Woynarowski JM. Dna strand breaks and apoptosis induced by oxaliplatin in cancer cells. Biochem Pharmacol. 2003; 66(2): 225–37.
5. Bang VJ, Kim YW, Yang HK, Chung HCH, Park Y.K, Lee KH et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012; 379(9813): 315-321.
6. Wang ZX, Yang XL, He MH, Wang F, Zhang DS, Li YH, et al. The Efficacy of Adjuvant FOLFOX6 for Patients with Gastric Cancer after D2 Lymphadenectomy. Medicine (Baltimore) 2016; 95(16): e3214.
7. Conroy T, Hammel P, Hebber M, Abdelghani MB, Wei AC, Raoul JL, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N Engl J Med. 2018; 379(25): 2395-2406.
8. André T, Boni C, Mounedji-boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer N Engl J Med. 2004: 350; 2343-2351.
9. André T, De Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-years survival and outcomes according to BRAF mutation and mismatch repair status of the mosaic study. J Clin Oncol. 2015; 33(35): 4176-4187.
10. Schiappacasse GV, Schiappacasse ED. Is Adjuvant Chemotherapy Efficient in Colon Cancer with High Microsatellite Instability? A Look Towards the Future. Cancer Res. 2019; 79(3): 441-444.
11. Al-Batran SE, Homann N, Schmalenberg H, Kopp HG, Haag GM, Luley KB, et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicenter, randomized phase 3 trial. J Clin Oncol. 2017; 35(15_suppl): 4004-4004.
12. Hospers G, Bahadoer RR, Dijkstra EA, Van Etten B, Marijnen C, Putter H, et al. Short-course radiotherapy followed by chemotherapy before TME in locally advanced rectal cancer: The randomized RAPIDO trial. J Clin Oncol. 2020; 38(15_suppl): 4006.
13. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. N Engl J Med. 2008; 358: 36-46.
14. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. N Engl J Med. 2011; 364: 1817-1825.
15. Colucci G, Gebbia V, Paoletti G, Giuliani F, Caruso, M, Gebbia N, et al. Phase III Randomized Trial of FOLFIRI Versus FOLFOX4 in the Treatment of Advanced Colorectal Cancer: A Multicenter Study of the Gruppo Oncologico Dell'Italia Meridionale. J Clin Oncol. 2005;

23: 4866-4875.

16. Alcindor T, Beauger N. Oxaliplatin: a review in the era of molecularly targeted therapy. Curr Oncol. 2011; 18(1): 18-25.

17. Tournigand Ch, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004; 22(2): 229-237.

18. Koutras AK, Makatsoris T, Paliogianni F, Kopsida G, Onyenadum A, Gogos CA, et al. Oxaliplatin-induced acute-onset thrombocytopenia, hemorrhage and hemolysis oncology. Oncology. 2004; 67(2): 179–182.

19. Zafar SY, Marcello JE, Wheeler JL, Rowe KL, Morse MA, Herndon JE, et al. Treatment-related toxicity and supportive care in metastatic colorectal cancer. J Support Oncol. 2010; 8(1): 15-20. PMID: 20235419.

20. Argyriou AA, Polychronopoulos P, Iconomou G, Chroni E, Kalofonos HP. A review on oxaliplatin-induced peripheral nerve damage. Cancer Treat Rev. 2008; 34: 368–77.

21. Jamieson S, Liu J, Connor B, Mckeage MJ. Oxaliplatin causes selective atrophy of a subpopulation of dorsal root ganglion neurons without inducing cell loss. Cancer Chemother Pharmacol. 2005; 56: 391–399.

22. Simpson D, Dunn Ch, Curran M. Goa, K.L. Oxaliplatin: a review of its use in combination therapy for advanced metastatic colorectal cancer. Drugs. 2003; 63(19): 2127-2156.

23. Imperia PS, Lazarus HM, Lass JH. Ocular complications of systemic cancer chemotherapy. Surv. Ophthalmol. 1989; 34(3): 209-230.

24. Noor A, Desai A, Singh M. Reversible Ocular Toxicity of Oxaliplatin: A Case Report. Cureus. 2019; 11(5): e4582. doi: 10.7759/cureus.4582.

25. Südhoff T, Enderle MD, Pahlke M, Petz C, Teschendorf C, Graeven U, et al.5-Fluorouracil induces arterial vasocontractions. Ann. Oncol. 2004; 15(4): 661-664.

26. Watson N, Al-Samkari H. Thrombotic and bleeding risk of angiogenesis inhibitors in patients with and without malignancy. JTH. 2021.

27. Brown M, Marmor M, Vaegan, Zrenner E, Brigell M, Bach M. ISCEV Standard for clinical electro-oculography (EOG). Doc Ophthalmol. 2006; 113: 205-212.

28. Noguchi Y, Kawashima Y, Kawara H, Tokuyama Y, Tamura Y, Uchiyama K, et al. A Retrospective Analysis of Eye Disorders Due to Oxaliplatin. Gan To Kagaku Ryoho 2015; 42(11): 1401-1405.

29. Naranjo CA, Bustos U, Sellers EM, Sandor P, Ruíz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981; 30(2): 239-245.

30. Mesquida M, Sánchez-Dalmau B, Ortiz-Pérez S, Pelegrín L, Molina-Fernández J.J, Figueroas-Roca M, et al. Oxaliplatin-Related Ocular Toxicity. Case Rep Oncol. 2010; 3(3): 423-427.

31. Ah-Thiane L, Raoul JL, Hiret S, Senellart H, Dumont F, Raimbourg J. Transient Vision Loss – A Rare Oxaliplatin-Induced Ophthalmologic Side Effect: A Report of Two Cases. Case Rep Oncol.2021; 14(1): 483-486.

32. Beaumont W, Sustronck P, Souied EH. A case of oxaliplatin-related toxic optic neuropathy. Journal Français d'Ophtalmologie 2021; 44(7): e393-e395.

33. Cavaletti G, Marmiroli P. Management of Oxaliplatin-Induced Peripheral Sensory Neuropathy. Cancers (Basel) 2020; 12(6): 1370.