European Journal of Cancer 112 (2019) 80–82

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Letter to the Editor

Vision loss after chemotherapy: an irinotecan-induced retinopathy

Alice Boilève [a,*], Mathieu Jozwiak [b], David Malka [a], Valérie Boige [a], Florence Le Roy [a], Michel Paques [c], Michel Ducreux [a]

[a] *Département de Médecine Oncologique, Gustave Roussy, Université Paris-Saclay, Paris, France*
[b] *Groupe Hospitalier Paris-Centre, Assistance Publique – Hôpitaux de Paris, Hôpital Cochin, Service de Médecine Intensive Réanimation, 27 Rue Du Faubourg Saint Jacques, Paris, France*
[c] *Département d'ophtalmologie, Hôpital des Quinze-Vingts, DHU SightMaintain, Centre d'investigation Clinique INSERM-DHOS 1423, Institut Hospitalo-Universitaire ForeSight, Paris, France*

Received 25 February 2019; accepted 27 February 2019
Available online 1 April 2019

KEYWORDS
Irinotecan;
Vision loss;
Toxicity;
Photoreceptors;
Retinopathy

Dear Editor,

Irinotecan is a topoisomerase-I inhibitor widely used to treat gastrointestinal tumours. Diarrhoea and neutropenia are well-known toxicities of irinotecan [1], whereas ophthalmological toxicity or vision loss has never been reported after irinotecan infusion.

Here, we report the case of a 53-year-old woman with a metastatic colon cancer, treated between 2011 and 2017 with 35 cycles of chemotherapy with 5-fluorouracil (5-FU), irinotecan and bevacizumab. Seven days after the 35th cycle of chemotherapy, the patient experienced a progressive bilateral vision loss with photophobia. Interestingly, the patient never received other concomitant medications, except for the usual antiemetics, during this chemotherapy cycle. Furthermore, the patient did not present any risk factors usually reported for ophthalmological toxicity such as diabetes mellitus, chronic kidney disease or hypertension [2].

Initially, visual acuity was 20/400 in both eyes. There was neither diplopia nor ptosis or relative afferent pupil defect. Slit lamp and fundus examinations were normal. Visual fields showed bilateral large central scotomas (Fig. 1A). Optical coherence tomography (OCT) indicated a diffuse loss of photoreceptors' outer segments (Fig. 1B). Adaptive optics ophthalmoscopy confirmed the absence of cone mosaic, uncovering the underlying retinal pigment epithelium monolayer (Fig. 1C). The diagnosis of retinopathy was, therefore, made.

Although irinotecan-induced retinopathy had never been described to our knowledge, irinotecan was still considered the most likely cause of this retinopathy, even if the patient never previously experienced any high-grade irinotecan-related toxicities. Indeed, the

* *Corresponding author.*
E-mail address: alice.boileve@gmail.com (A. Boilève).

https://doi.org/10.1016/j.ejca.2019.02.015

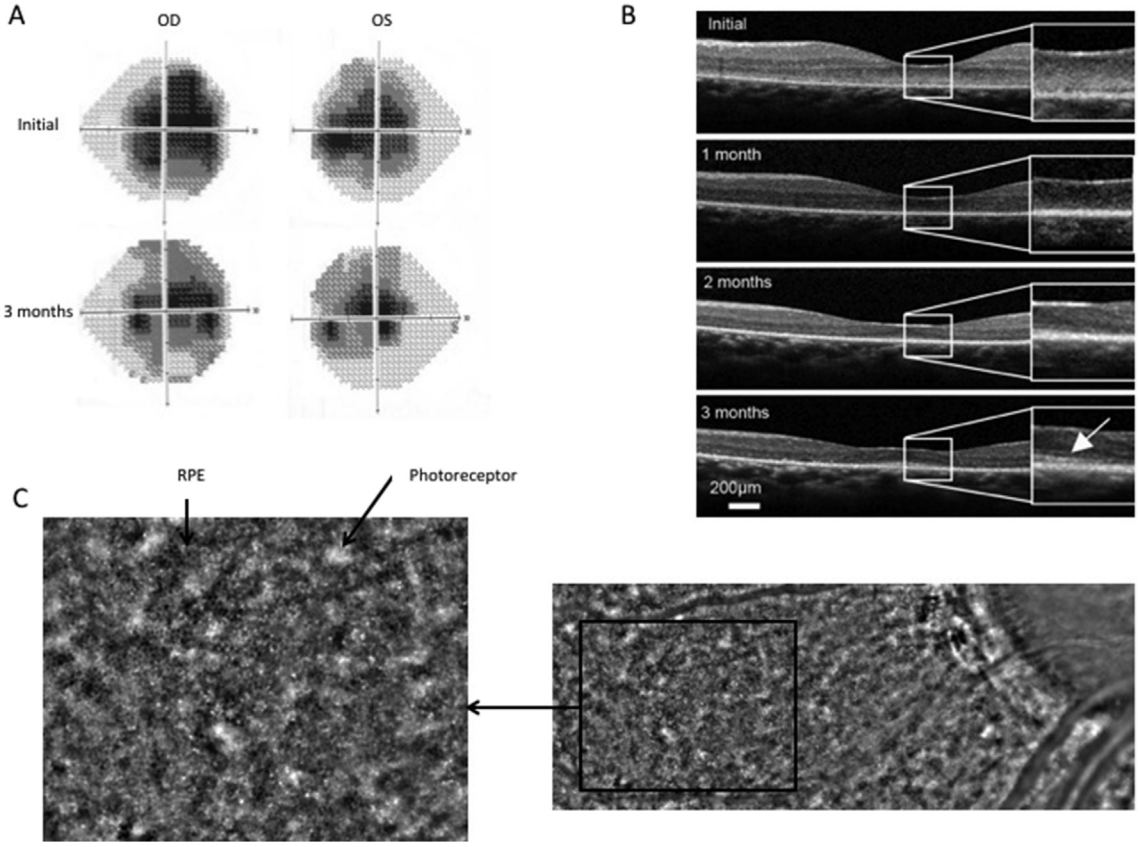

Fig. 1. A. Evolution of visual fields at initial examination (upper panel) and three months after stopping irinotecan (lower panel), showing the improvement of the large central scotoma in both eyes. B. Evolution of optical coherence tomographies. At initial examination, the inner/outer segment line and cone outer segment line appeared blurry in both eyes. The follow-up examinations after stopping irinotecan showed recovery of the central outer segments (arrow). C. Adaptive optics ophthalmoscopy image at initial examination. The absence of cone mosaic and the visibility of the underlying retinal pigment epithelium (RPE) monolayer (black dots) indicated the loss of the highly reflective outer segments.

ophthalmological toxicity of fluoropyrimidine [2,3] and bevacizumab, even by the intraocular route [2,4], is well documented and does not include retinopathy. Thus, irinotecan was stopped after a specialised ophthalmological advice and capecitabine (an oral 5-FU pro-drug) only was continued. A progressive recovery of retinopathy was then observed, with improvement of visual acuity, visual fields and OCTs (Fig. 1B). Three months after stopping irinotecan, visual acuity was 20/20 in both eyes despite reduced but persisting central scotomas on the visual field (Fig. 1A). The OCT showed a recovery of central photoreceptors' outer segments only with persistent peripheral outer segments defects (Fig. 1B).

Vision loss secondary to retinopathy is a class effect of some targeted therapies such as MEK inhibitors [5,6], but an extremely rare ophthalmological toxicity of chemotherapy [7–11] was only reported with cisplatin, gemcitabine and docetaxel. As far as we know, we report the first case of reversible irinotecan-induced retinopathy, even if we cannot exclude with certainty that the vision loss experienced by the patient might also be related to the cumulative doses and/or the combined use of the three drugs. However, it is of importance to note that, because the patient recovered normal visual acuity under capecitabine, it is very unlikely that fluoropyrimidines were involved in this ophthalmological toxicity.

The mechanisms of this suspected irinotecan-induced retinopathy remain to be elucidated. Irinotecan is a topoisomerase I inhibitor known to cross the hematoencephalic barrier [1], hence possibly the blood-retinal barrier. Thus, irinotecan could potentially induce ophthalmological toxicity. In this regard, a recent study suggests that irinotecan can alter the photoreceptor development [12]. Interestingly, the functional and anatomical ophthalmological recovery indicates that irinotecan impaired the capability of rods and cones photoreceptors to generate outer segments. The normal-appearing retinal pigment epithelial layer and the absence of pigment mottling argue against retinal pigment epithelial dysfunction. The complete recovery of the central visual acuity suggests that most foveal cones survived the toxic

episode. Nevertheless, the survival of rods cannot be ascertained because scotopic function was not specifically assessed.

Irinotecan-related toxicities can be potentiated by UGT1A1 polymorphisms (UGT1A1*28 and UGT1A1*6 mutations notably) [1], which are responsible for the Gilbert syndrome, characterised by intermittent hyperbilirubinemia. Because irinotecan is detoxified by UGT1A1 enzyme, the perfusion of irinotecan in patients with UGT1A1 polymorphisms can unmask a Gilbert syndrome and induces, in most cases, high-grade irinotecan toxicities, in particular haematological and digestive toxicities with severe neutropenia and/or profuse diarrhoea. Because this patient never experienced any clinical or biological signs of Gilbert syndrome or any high-grade irinotecan toxicities during the 35 cycles of chemotherapy, an association between UGT1A1 polymorphisms and the potential ophthalmological toxicity of irinotecan we described here seems to be unlikely.

Finally, because this ophthalmological toxicity was observed after the 35th cycle of chemotherapy, a cumulative dose-dependent or time-dependent toxicity of irinotecan cannot be ruled out. To further investigate and better characterise the evolution of this unknown toxicity, it might be of interest to perform regular ophthalmological follow-up with OCTs in patients receiving multiple cycles of irinotecan.

To conclude, vision loss induced by retinopathy is an extremely rare ophthalmological side-effect of chemotherapy. Here, we report the first potential case of reversible irinotecan-induced retinopathy. Further studies are required to better characterise the physiopathology and the evolution of this unknown toxicity of irinotecan.

Conflict of interest statement

None declared.

References

[1] de Man FM, Goey AKL, van Schaik RHN, Mathijssen RHJ, Bins S. Individualization of irinotecan treatment: a review of pharmacokinetics, pharmacodynamics, and pharmacogenetics. Clin Pharmacokinet 2018. https://doi.org/10.1007/s40262-018-0644-7.

[2] Schmid KE, Kornek GV, Scheithauer W, Binder S. Update on ocular complications of systemic cancer chemotherapy. Surv Ophthalmol 2006;51:19–40. https://doi.org/10.1016/j.survophthal.2005.11.001.

[3] Shapiro MS, Thoft RA, Friend J, Parrish RK, Gressel MG. 5-Fluorouracil toxicity to the ocular surface epithelium. Investig Ophthalmol Vis Sci 1985;26:580–3.

[4] Ghasemi Falavarjani K, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. Eye (Lond) 2013;27:787–94. https://doi.org/10.1038/eye.2013.107.

[5] Urner-Bloch U, Urner M, Jaberg-Bentele N, Frauchiger AL, Dummer R, Goldinger SM. MEK inhibitor-associated retinopathy (MEKAR) in metastatic melanoma: long-term ophthalmic effects. Eur J Cancer 2016;65:130–8. https://doi.org/10.1016/j.ejca.2016.06.018.

[6] Stjepanovic N, Velazquez-Martin JP, Bedard PL. Ocular toxicities of MEK inhibitors and other targeted therapies. Ann Oncol 2016;27:998–1005. https://doi.org/10.1093/annonc/mdw100.

[7] Gonzalez F, Menendez D, Gomez-Ulla F. Monocular visual loss in a patient undergoing cisplatin chemotherapy. Int Ophthalmol 2001;24:301–4.

[8] Hilliard LM, Berkow RL, Watterson J, Ballard EA, Balzer GK, Moertel CL. Retinal toxicity associated with cisplatin and etoposide in pediatric patients. Med Pediatr Oncol 1997;28:310–3.

[9] Katz BJ, Ward JH, Digre KB, Creel DJ, Mamalis N. Persistent severe visual and electroretinographic abnormalities after intravenous Cisplatin therapy. J Neuro Ophthalmol 2003;23:132–5.

[10] Kord Valeshabad A, Mieler WF, Setlur V, Thomas M, Shahidi M. Posterior segment toxicity after gemcitabine and docetaxel chemotherapy. Optom Vis Sci 2015;92:e110–3. https://doi.org/10.1097/OPX.0000000000000571.

[11] Kovach JL. Gemcitabine-induced retinopathy. Retin Cases Brief Rep 2018;12:240–1. https://doi.org/10.1097/ICB.0000000000000471.

[12] Campbell LJ, West MC, Jensen AM. A high content, small molecule screen identifies candidate molecular pathways that regulate rod photoreceptor outer segment renewal. Sci Rep 2018;8:14017. https://doi.org/10.1038/s41598-018-32336-y.