CASE REPORT

Single-eye trial of a topical carbonic anhydrase inhibitor versus intravitreal bevacizumab for the treatment of taxane drug-induced cystoid macula oedema

Mark M Hassall,¹ Nicholas Howard Andrew²¹Nuffield Laboratory of Ophthalmology, University of Oxford, Oxford, UK²Department of Medicine, Royal Adelaide Hospital, Adelaide, South Australia, Australia**Correspondence to**
Dr Mark M Hassall,
m.hassall@gmail.com

Accepted 5 April 2016

SUMMARY

Taxanes are a class of microtubule stabilising agents used to treat a wide range of malignancies. Taxane drug-induced cystoid macula oedema (TDICMO) is a known but rare complication of therapy. First reported with Docetaxel in 2003 and Paclitaxel in 2007, there are currently less than 20 cases of TDICMO in the literature. Although most cases resolve following taxane cessation, several authors have tried using carbonic anhydrase inhibitors or intravitreal bevacizumab to accelerate resolution or when taxane therapy cannot be discontinued. We report the first published case of TDICMO treated with a single-eye trial of topical dorzolamide versus intravitreal bevacizumab.

CASE REPORT

A 73-year-old Caucasian man with stage 4C hypopharyngeal cancer (T3N2cM1) presented with slowly progressive bilateral vision loss of 2 months' duration. Ocular history included primary open angle glaucoma and left pseudophakia. Other medical history included hypercholesterolaemia, hypertension, ischaemic heart disease, gout and asthma. Medications included bimatoprost 0.03% eye drop nocte (duration 9 years), buprenorphine patch 10 µg/h weekly, dexamethasone tablet 0.5 mg daily, aspirin 100 mg daily, atenolol 50 mg daily, atorvastatin 40 mg daily, perhexiline maleate 200 mg daily, pantoprazole 40 mg daily, prazosin 1 mg daily. At presentation, the patient had just completed his fifth one-monthly cycle of intravenous protein-bound nab-Paclitaxel (Abraxane; Colgene Corporation, New Jersey, USA) dosed at 90 mg/m², co-administered with intravenous carboplatin.

On examination, pinhole visual acuity (VA) was 6/38 in the right eye and 6/15 in the left (table 1). Anterior segment examination showed left eye pseudophakia but was otherwise unremarkable. Funduscopy revealed bilateral cystoid macular oedema (CMO). Optical coherence tomography (OCT) demonstrated central macula thicknesses (CMT) of 526 µm in the right eye and 461 µm in the left. Fundus fluorescein angiogram (FFA) revealed no vascular leakage (figure 1). There were no signs of systemic fluid retention on physical examination. The patient's bilateral CMO was attributed to his bimatoprost eye drops. The bimatoprost was stopped and the patient was started on

ketorolac 0.5% eye drops four times a day in both eyes.

One month later, the patient's pinhole VA had deteriorated to 6/48 in the right eye and 6/19 in the left. OCT revealed CMT of 658 µm in the right eye and 626 µm in the left. The patient had just completed his sixth and final cycle of nab-Paclitaxel and carboplatin. The patient was diagnosed with Taxane Drug Induced Cystoid Macula Oedema (TDICMO).

Informed consent was obtained to randomise one eye to monthly injections of intravitreal bevacizumab (Avastin, Roche Products, New South Wales, Australia) and the other eye to dorzolamide 2% eye drops (Trusopt, Merck, Sharp & Dohme, New South Wales, Australia) three times daily. The left eye was randomised to the bevacizumab arm by coin toss and treatment was started on that visit. The patient was reviewed at day 7, day 14, day 30 and day 60. The visual acuity and OCT data are presented in table 1. The OCT images (figure 2) show a profound improvement over time. Percentage improvement in pinhole VA closely mirrored percentage reduction in CMT over time. The patient tolerated treatment well and no complications were reported.

DISCUSSION

This is the first published single-eye trial comparing a topical carbonic anhydrase inhibitor to intravitreal bevacizumab for the treatment of TDICMO. The results are moderately confounded by the two eyes having different visual acuity and CMT at day zero. However, the relative improvement in visual acuity and CMT in each eye was approximately equal in magnitude and time course.

As such, the results of this case do not support the use of intravitreal bevacizumab, an invasive treatment with a small risk of serious complications, over topical Dorzolamide in the treatment of TDICMO.

TDICMO is a 'non-leaking' form of macular oedema and there are fewer than 20 case reports in the literature.^{1–12} It is characterised by the absence of macular hyperfluorescence on FFA despite gross macular thickening. Indocyanine green angiography was not performed in our case but has been reported to be normal in previous case reports.¹² Patients present with a gradual decline in visual acuity over several months, which is typically

CrossMark

To cite: Hassall MM, Andrew NH. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-212733

Table 1 Pinhole VA and CMT at presentation and follow-up

	Right eye (dorzolamide 2% TDS)					Left eye (bevacizumab 1.25 mg monthly)				
	Pinhole VA (Snellen)	Pinhole VA (LogMAR)	% Change LogMAR VA from day 0	CMT (μm)	% Change CMT from day 0	Pinhole VA (Snellen)	Pinhole VA (LogMAR)	% Change LogMAR VA from day 0	CMT (μm)	% Change CMT from day 0
Day 0*	6/48	0.9		658		6/19	0.5		626	
Day 7	6/38	0.8	+11.1	597	−9.3	6/19	0.5	0	580	−7.3
Day 14	6/38	0.8	+11.1	649	−1.4	6/19	0.5	0	588	−6.1
Day 30*	6/24	0.6	+33.3	492	−25.2	6/9.5	0.2	+60	429	−31.5
Day 60	6/12	0.3	+66.7	303	−54.0	6/9.5	0.2	+60	299	−52.3

*Intravitreal bevacizumab injection given.

%, per cent; CMT, central macula thicknesses; TDS, three times a day; VA, visual acuity.

bilateral but may be asymmetric. The evolution of examination features may rarely lag behind the fellow eye by up to 12 months.⁵

Taxanes are a class of chemotherapy agents that bind to microtubuli in the cytoskeleton of cells and inhibit microtubule remodelling. Their therapeutic effect is to impair mitosis in rapidly cancer dividing cells, but they also disrupt the normal interaction between the extracellular matrix and cellular cytoskeleton. It has recently been discovered that this interaction is important in regulating tissue interstitial pressure and thereby the extravasation of fluid from capillaries.¹³ Accordingly, a common side effect is peripheral oedema, which can be severe.¹⁴

The mechanism of TDICMO is unknown but is postulated to involve impaired intracellular transport within retinal pigment epithelium cells, reducing the absorption of fluid from the neurosensory retina.¹² Alternatively, microtubule disruption may render the blood-retinal barrier more permeable to small molecules like H₂O, without affecting barrier function to larger molecules like fluorescein.⁵ Both of these postulated mechanisms can explain macular oedema without leakage on FFA.

There is some evidence that xanthophylls act as endogenous microtubule stabilising agents in the primate retina, sharing the same tubulin binding site as paclitaxel.¹⁵ However, it has not been investigated whether manipulation of the carotenoid pathway alters the natural history of TDICMO. There have been several reports of TDICMO developing despite concurrent systemic bevacizumab being used as a chemotherapeutic,^{6 12} indicating that the mechanism of TDICMO is independent of the vascular endothelial growth factor pathway.

Treatments that have been used for TDICMO include: systemic or topical carbonic anhydrase inhibitors (CAI), topical anti-inflammatory agents, intravitreal bevacizumab and cessation of taxane therapy. To the best of our knowledge, there are no other reports comparing the efficacy of different pharmacotherapies. There is a single report of unilateral topical dorzolamide accelerating CMO resolution compared to the untreated fellow eye;¹⁶ however, the comparative trial was terminated early. Intravitreal bevacizumab and systemic acetazolamide have been the most commonly used treatments for TDICMO, but both can be associated with significant morbidity.

Figure 1 Fundus fluorescein angiogram of the left eye. Showing colour (top left), autofluorescence (top right), early stage (bottom left) and late stage (bottom right). Note the absence of late stage fluorescein leakage typical of CMO. CMO, cystoid macular oedema.

Figure 2 Optical coherence tomography before and after therapy. Demonstrates macular oedema in both retinas before therapy and profound resolution 2 months later.

The latest meta-analysis of intravitreal bevacizumab trials reported multiple adverse events including endophthalmitis (<1%), retinal detachment (0–29%), ocular haemorrhage (0–72%), visual loss (0–50%), stroke (0–8.7%) and myocardial infarction (0–8.2%).¹⁷ CAIs can cause severe acidosis, renal calculi, encephalopathy, Stevens-Johnson syndrome, haemolytic anaemia, and blood dyscrasias including aplastic anaemia.¹⁸

In all case reports of TDICMO, regardless of the concurrent therapy, complete resolution of oedema occurred within 4–10 weeks of ceasing taxane chemotherapy. Patients unable to cease the taxane usually have persistent CMO,¹⁰ although some case reports have shown resolution or stabilisation of CMO with the addition of a systemic CAI.^{5 19} Visual acuity usually, but not always, returns to baseline.

There are limitations to a single eye trial of topical dorzolamide versus intravitreal bevacizumab. Specifically, results from single patient studies may lack generalisability. Furthermore, each eye had a different visual acuity and CMT at the start of the trial, which confounds interpretation of the results. Finally, it is known that intravitreal bevacizumab is exported from the eye and significantly lowers serum vascular endothelial growth factor levels.²⁰ It is possible that intravitreal bevacizumab had a therapeutic effect on the fellow eye, as has been reported in case series of bilateral diabetic macular oedema and in case reports of bilateral branch retinal vein occlusions and bilateral uveitis-related macular oedema.²¹ However, the contralateral

bevacizumab treatment effect observed in our patient is eight-fold smaller than the mean reduction in untreated eye CMT reported in previous research.

Future studies could aim to corroborate our finding with a larger patient sample, although the rarity of TDICMO will inevitably limit cohort size. Other areas for future research include a trial of topical dorzolamide versus placebo after cessation of taxane therapy, systemic CAI therapy versus concurrent topical and systemic CAI therapy and whether carotenoid supplementation can displace taxanes from binding to retinal cells.

Learning points

- ▶ Treatment with a systemic or topical carbonic anhydrase inhibitor appears to be of benefit.
- ▶ Our results do not support the use of intravitreal bevacizumab over topical dorzolamide.
- ▶ Cessation of taxane chemotherapy is likely to be the most effective intervention.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Teitelbaum BA, Tresley DJ. Cystic maculopathy with normal capillary permeability secondary to docetaxel. *Optom Vis Sci* 2003;80:277–9.
- Joshi MM, Garretson BR. Paclitaxel maculopathy. *Arch Ophthalmol* 2007;125:709–10.
- Ito S, Okuda M. [A case of cystic maculopathy during paclitaxel therapy]. *Nippon Ganka Gakkai Zasshi* 2010;114:23–7.
- Ham DS, Lee JE, Kim HW, et al. A case of cystoid macular edema associated with Paclitaxel chemotherapy. *Korean J Ophthalmol* 2012;26:388–90.
- Koo NK, Kim YC. A case of paclitaxel-induced maculopathy treated with methazolamide. *Korean J Ophthalmol* 2012;26:394–7.
- Baskin DE, Garg SJ. Abraxane-induced cystoid macular edema refractory to concomitant intravenous bevacizumab. *Can J Ophthalmol* 2011;46:200–1.
- Georgakopoulos CD, Makri OE, Vasilakis P, et al. Angiographically silent cystoid macular oedema secondary to paclitaxel therapy. *Clin Exp Optom* 2012;95:233–6.
- Tanaka Y, Bando H, Hara H, et al. Cystoid macular edema induced by nab-paclitaxel. *Breast Cancer* 2015;22:324–6.
- Smith SV, Benz MS, Brown DM. Cystoid macular edema secondary to albumin-bound paclitaxel therapy. *Arch Ophthalmol* 2008;126:1605–6.
- Rahman HT, Yeh S, Bergstrom CS. Cystoid macular edema without leakage secondary to nab-Paclitaxel (Abraxane): clinical experience with intravitreal bevacizumab. *J Ocul Pharmacol Ther* 2013;29:360–2.
- Hauck MJ, Purvin VA. Paclitaxel maculopathy. *Neuro Ophthalmol* 2011;35:147–50. <http://informahealthcare.com/doi/abs/10.3109/01658107.2011.580889>
- Kuznetcova TI, Cech P, Herbert CP. The mystery of angiographically silent macular oedema due to taxanes. *Int Ophthalmol* 2012;32:299–304.
- Brønstad A, Berg A, Reed RK. Effects of the taxanes paclitaxel and docetaxel on edema formation and interstitial fluid pressure. *Am J Physiol Heart Circ Physiol* 2004;287:H963–8.
- Ohsumi S, Shimozuma K, Ohashi Y, et al. Subjective and objective assessment of edema during adjuvant chemotherapy for breast cancer using taxane-containing regimens in a randomized controlled trial: the National Surgical Adjuvant Study of Breast Cancer 02. *Oncology* 2012;82:131–8.
- Crabtree DV, Ojima I, Geng X, et al. Tubulins in the primate retina: evidence that xanthophylls may be endogenous ligands for the paclitaxel-binding site. *Bioorg Med Chem* 2001;9:1967–76.
- Ehlers JP, Rayess H, Steinle N. Topical dorzolamide therapy for taxane-related macular oedema. *Eye (Lond)* 2013;27:102–4.
- Poku E, Rathbone J, Wong R, et al. The safety of intravitreal bevacizumab monotherapy in adult ophthalmic conditions: systematic review. *BMJ Open* 2014;4:e005244.
- Swenson ER. Safety of carbonic anhydrase inhibitors. *Expert Opin Drug Saf* 2014;13:459–72.
- Meyer KM, Klink T, Ugurel S, et al. Regression of paclitaxel-induced maculopathy with oral acetazolamide. *Graefes Arch Clin Exp Ophthalmol* 2012;50:463–4.
- Avery RL, Castellarin AA, Steinle NC, et al. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD. *Br J Ophthalmol* 2014;98:1636–41.
- Hanhart J, Tiosano L, Averbukh E, et al. Fellow eye effect of unilateral intravitreal bevacizumab injection in eyes with diabetic macular edema. *Eye* 2014;28:646–53.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow