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Properties and clinical utility of topotecan fluorescence: uses for retinoblastoma

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ABSTRACT

Topotecan fluoresces when exposed to ultraviolet (UV) light. Our observations with UV light in retinoblastoma cases has allowed us to minimise and manage inadvertent skin contact, guide periocular injections and leakage from such injections and document conjunctival contact after periocular injection in addition to demonstrating the drug in the vitreous after intravitreal injection. The technique is safe, inexpensive and easy to perform.

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Topotecan is a Food and Drug Administration approved chemotherapeutic agent that has been used (off-label) in the treatment of intraocular retinoblastoma through the intrarterial,[1] periocular[2] and intravenous[3] route (and investigated as an intravitreal agent[4 5]), in addition to use in patients with metastatic retinoblastoma.[6] With an excitation wavelength of 370 nm and an emission at 520 nm, topotecan is readily visible with fluorescent light. Using Wood's lamp (also known as 'black light', but in reality ultraviolet (UV)-A light) the drug can be seen and even quantified in the lab. These lamps have a violet filter and are not hazardous to human skin or eyes because of the low power. They are readily accessible: a handheld portable UV black light is available for online purchase for less than $10.

We have recently used this method during periocular, subconjunctival and intravitreal delivery of topotecan, which allowed us to make observations not apparent to the naked eye. This enhanced visualisation of topotecan through fluorescence has important clinical implications for safety and for understanding clinical efficacy based on appropriate placement of the drug.

VISUALISATION FOR PROPER HANDLING OF THE DRUG

Topotecan can cause skin changes including severe irritation, and should this occur, it is advised to wash the skin immediately. In a prospective study of women receiving systemic topotecan for treatment of malignancies, 15% of patients were determined to have skin toxicity manifested by palmoplantar erythodysesthesia.[7] In extreme cases, topotecan can induce a cellulitis-like drug reaction.[8] The drug manufacturer cautions the handler to wear suitable gear to prevent skin contact.

Although topotecan is a clear solution to the naked eye (figure 1A), with a Wood's lamp it is easily visible within a plastic syringe (figure 1B). If any of the drug has leaked out into the needle cap it can be seen (figure 1C) and if it drips onto skin, it can be found (figure 1D) and removed with appropriate protective gear. The enhanced visualisation of topotecan via fluorescence allows for improved handling of the drug, and identifies potential events that could result in toxicity from direct contact to patients and healthcare personnel.

VISUALISATION OF SKIN CONTACT FOR MANAGEMENT OF THE PATIENT

In some clinical instances, skin contact with topotecan is unavoidable. However, the fluorescent properties of topotecan allows for the detection and appropriate management of these occurrences, with the intention of limiting toxic outcomes. For example, injection of topotecan into the subconjunctival space (figure 2A) can result in retrograde flow of the drug through the needle tract, expulsion of the drug into the tear film (figure 2B) and leakage onto the eyelid and periocular dermis (figure 2C). This has the potential of skin toxicity and symptomatic consequences for the patients. In our clinical practice, we identify escaped topotecan with the Wood's lamp and pay particular attention to collecting the contaminated effluent. We clean and irrigate the contaminated skin with balanced salt solution to limit exposure to the drug and recheck fluorescence after such manoeuvres.

VISUALISATION OF DRUG PLACEMENT INTO THE TARGET COMPARTMENT OF THE EYE

Fluorescent visualisation of topotecan highlights the eye compartment in which the drug was injected, and provides valuable clinical information. Periocular injections are done by starting 4 mm from the limbus employing a 25 g 1.5 inch primed needle. The needle is then pushed posteriorly hugging the surface of the globe and avoiding the inferior oblique muscle before injecting. The injection is not designed to be a subconjunctival injection and if placement is adequate, then during injection with Wood's light viewing, no drug should be visible (figure 3A). Alternatively, a subconjunctival injection will show fluorescence and pooling of the drug as it exits the puncture site (figure 2). Upon removing the emptied syringe, the drug is still visible in the syringe and the small amount of drug on the needle tip will 'coat' the needle puncture demonstrating a bright non-enlarging spot (figure 3C). Within 2 min increased fluorescence can be seen in the vitreous (figure 3D) indicating rapid passage across the sclera, through the choroid and retina. Conceivably, injecting in a sub-Tenon fashion may allow closer apposition of the drug to the posterior/peripapillary and macular scleral surface in comparison to a subconjunctival injection, and result in better drug transference to the vitreous cavity.

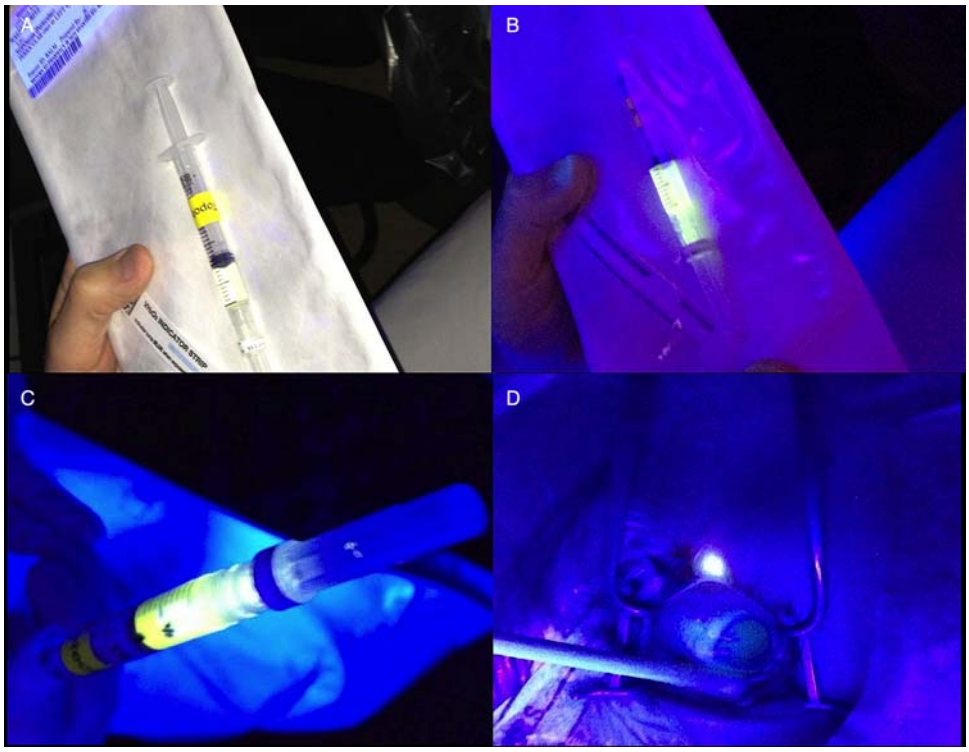

Figure 1 (A–D) Fluorescence of topotecan under Wood's lamp viewing.

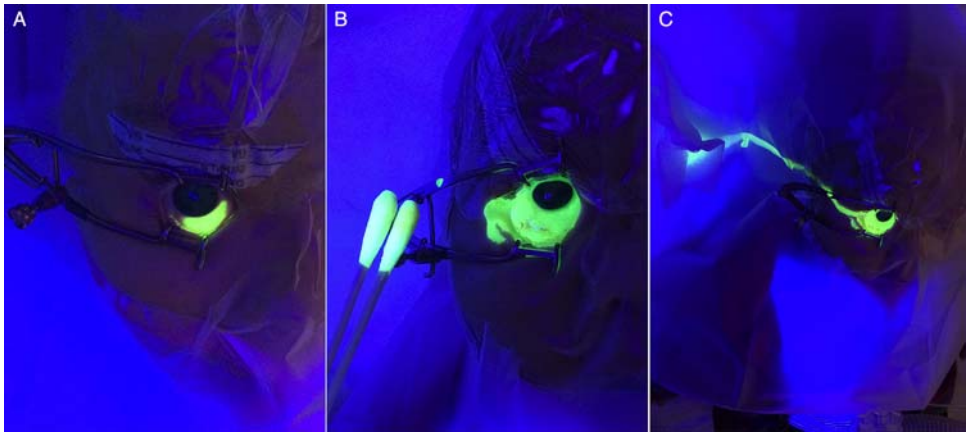

Figure 2 (A–C) Visualisation of subconjunctival topotecan injection under Wood's lamp viewing.

When topotecan is injected intravitreally it can easily be detected in the vitreous because of its fluorescence with UV light. Seconds after injecting intravitreal topotecan at the 10 o'clock meridian, the drug can be seen in the superotemporal quadrant of the eye with slow diffusion in the vitreous cavity (see figure 4 and online supplementary video 1). This allows the clinician to visualise the highest concentration of the drug minutes after injection, sense the pattern of drug distribution and tailor future injections based on geographical burden of disease. When an eye is injected with separate injections of

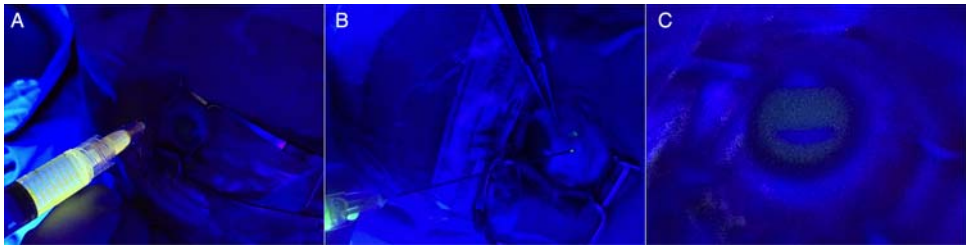

Figure 3 (A–C) Visualisation of sub-Tenon topotecan injection under Wood's lamp viewing.

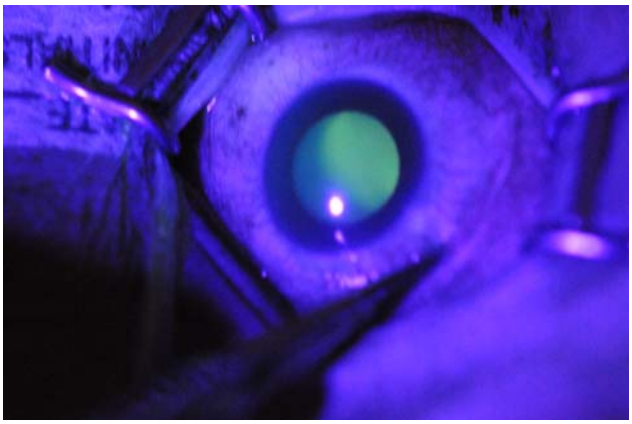

Figure 4 Visualisation of intravitreal topotecan injection under Wood's lamp viewing.

topotecan and melphalan, the topotecan fluoresces as expected, while the melphalan fails to fluoresce.

DISCUSSION

Topotecan is approved for the treatment of metastatic ovarian carcinoma and small cell lung cancer after failure with other agents in addition to being used for recurrent/persistent cervical carcinoma.[9] It is a topoisomerase inhibitor and a semisynthetic derivative of camptothecin—a natural product extracted from the bark of the tree *Camptotheca acuminata*. It creates single strand DNA, breaks and intercalates DNA, preventing DNA replication. Topotecan has the valuable property of emitting fluorescence and being readily visible with a Wood's lamp. This is of particular concern since skin contact with topotecan is associated with toxicity.

Thus, use of Wood's lamp when preparing or delivering ocular topotecan may allow for safer delivery of drug by identifying leakage on the skin, help guide physicians when injecting to confirm placement of the drug (for instance, a sub-Tenon as opposed to subconjunctival location) and provide a visual distribution of the drug, particularly during intravitreal injections, for future injection planning. This is an accessible technique that requires easily replicable minimal resources and has meaningful clinical utility.

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Competing interests None.

Patient consent Obtained.

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Notes