REVIEW

Visual Pathway Degeneration in Chemotherapy-Related Neurotoxicity: A Review and Directions for Future Research

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ABSTRACT

Chemotherapy-related neurotoxicity (CRNT) is an emerging public health concern. Visual pathway degeneration may be a symptom of CRNT. We surveyed the current literature for evidence of visual pathway degeneration in cancer patients receiving chemotherapy. A systematic review was conducted in PubMed. Six published articles met our inclusion criteria. The studies showed reduced retinal thickness, primarily in the retinal nerve fibre layer, and impaired inner retinal function in patients receiving chemotherapy. In summary, the current literature suggests chemotherapy may induce visual pathway degeneration. Future research may benefit from improving study design, exploring mechanisms of chemotherapy-related visual pathway degeneration, and incorporating these findings into biomarker development.

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Introduction

Chemotherapy-related neurotoxicity

Advances in chemotherapy efficacy have led to continuous improvements in cancer survival over the last 25 years. In turn, improved cancer survival and consistent population growth contribute to our growing cancer survivor population, which is expected to grow by 29.1% to 21.7 million by 2029.¹ Despite improvements in cancer survival, chemotherapy-related toxicities remain a concern for patients and physicians. Chemotherapy-related neurotoxicity (CRNT), which impairs central nervous system (CNS) function in over 50% of cancer survivors, produces a range of symptoms including pain, fatigue, sensory neuropathy, and cognitive dysfunction.^{2,3} Given CNS involvement in nearly every activity of daily living, CRNT can negatively impact cancer survivor long-term quality of life. Developing research programmes aimed at detecting and preventing CRNT is therefore paramount.

Neural mechanisms of CRNT remain largely unknown. Previous reviews of neuroimaging studies have described consistent patterns of chemotherapy-related changes in brain structure and function across

multiple cortical regions, including frontal, parietal, and temporal cortices.^{4,5} Neuroimaging technologies have primarily been used to describe patterns of cognitive dysfunction commonly reported in cancer patients receiving chemotherapy.⁶ Chemotherapy-related cognitive dysfunction likely emerges from similar underlying mechanisms contributing to other symptoms of CRNT.⁷ For example, chemotherapy-induced systemic inflammation has been shown to activate neuroinflammatory pathways.^{8,9} Similar neuroinflammatory pathways have been implicated in neurodegenerative disease,¹⁰ suggesting CRNT may share a common pathophysiological pathway with other neurodegenerative diseases.^{11–13} Further exploration into the full range of CRNT pathophysiology will continue to inform research programmes aimed at detecting and preventing CRNT.

An unexplored hypothesis proposes a study of visual pathway degeneration as a paradigm to explain patterns of cognitive impairment in cancer survivors.¹⁴ This hypothesis suggests that visuo-retinal impairments may accompany and, more broadly, be a marker of dysfunctional brain activity. In their review, Raffa and Tallarida described multiple studies demonstrating significant deficits in cognitive

domains that require normal visual function. Further supporting this hypothesis, previous reviews of primarily clinical case reports have revealed consistent patterns of chemotherapy-associated ocular toxicities due to multiple agents.^{15,16} If visual pathway degeneration is a valid marker of dysfunctional brain activity, then research programmes aimed at detecting and preventing CRNT may benefit from utilising ophthalmic biomarkers. Indeed, several ophthalmic measures have shown promise in tracking disease progression in neurodegenerative diseases.^{17–21} The purpose of the current work is to survey ophthalmic biomarkers that can be used in CRNT research, provide a systematic review of literature demonstrating chemotherapy-related changes in ophthalmic biomarkers, and offer suggestions for future research to explore visual pathway degeneration in CRNT.

An overview of ophthalmic biomarkers

The neurosensory retina, being an outpost of the brain,²² offers an elegant model for studying neural circuits in health and disease.²³ The retina is comprised of three nuclear layers containing cell bodies of distinct neuronal populations and two layers containing synaptic processes between each nuclear layer. The outer nuclear layer contains cell bodies of rods and cones, which selectively respond to varying degrees of light intensity and wavelengths (i.e. colours). The inner nuclear layer contains cell bodies of bipolar, horizontal, and amacrine cells, which selectively modulate neural activity transmitted by photoreceptors through excitatory and inhibitory interactions. The ganglion cell layer contains cell bodies of ganglion cells, which relay neural activity from the retina to the brain via ganglion cell axons within the retinal nerve fibre layer (RNFL) through the optic nerve. Synaptic processes between the photoreceptors and bipolar cells make up the outer plexiform layer, and synaptic processes between bipolar cells and ganglion cells make up the inner plexiform layer. Ophthalmic biomarkers have been developed and incorporated into clinical practice to evaluate the structure and function of these distributed retinal populations.

Optical coherence tomography (OCT) provides micrometre-level structural resolution of the retina. Acquisition protocols commonly include structural images with a relatively small field of view centred

over two retinal landmarks: macula and optic disc. Structural parameters obtained for the macula, which contains the highest density of photoreceptor cell bodies and contributes to central vision processing, include average thickness and total volume across all retinal layers. Structural parameters for the optic disc, where ganglion cell axons within the RNFL converge to form the optic nerve and exit point from the retina to the brain, include RNFL thickness. More recently, software packages have been developed to obtain structural parameters individually for each retinal layer,^{24,25} allowing for more robust investigations of fine-scale changes in retinal cell populations. Retina structural parameters provided by OCT share homologies with brain structural parameters obtained through magnetic resonance imaging (MRI). MRI structural parameters commonly include global and regional grey and white matter volumes, which correspond to total volume of neuronal cell bodies and axonal processes, respectively. Correspondingly, OCT techniques are able to measure neuronal cell body and axonal thickness and volume parameters from the macula and optic disc. Numerous studies have demonstrated reduced grey and white matter volumes in CRNT.^{26,27} An increasing number of studies demonstrate correlations between OCT and MRI structural parameters that may be used to track neurodegenerative disease progression.^{19–21} For example, Mutlu and colleagues found reduced RNFL thickness was associated with smaller grey and white matter volumes in frontal, temporal, and occipital cortices.¹⁹ Thus, OCT may prove to be sensitive to global changes in brain structure commonly reported in CRNT.

Electroretinography (ERG) provides millisecond-level functional resolution of distinct retinal populations. ERG is recorded from corneal electrodes in either scotopic or photopic conditions to isolate rod and cone pathways, respectively. ERG amplitude modulations following a brief light stimulus reveal functional properties of specific retinal populations. Photoreceptor function can be characterised by the a-wave,^{28,29} a large negative deflection in ERG amplitude that peaks as early as 5–10 milliseconds following light stimulation. Oscillatory potentials (OP), a series of high-frequency low-amplitude deflections that peak approximately 50 milliseconds following light stimulation, characterise amacrine cell function,³⁰ though the origin of OP signalling

remains a matter of debate. Bipolar cell function can be characterised by the b-wave,³¹ a large positive deflection in ERG amplitude that peaks as early as 40 milliseconds following light stimulation. More sophisticated light stimulation protocols have recently been developed to assess the function of other retinal populations, including ganglion cells.³² Visual evoked potentials (VEP) measure the electrical activity generated by striate and extrastriate visual cortex following light stimulation using posterior scalp electrodes.³³ VEP abnormalities in the absence of ERG abnormalities are suggestive of visual pathway degeneration outside of the retina in either the optic nerve or visual cortex. In contrast, VEP abnormalities with ERG abnormalities are suggestive of visual pathway degeneration in at least the retina, with possible additional pathology in the optic nerve and visual cortex. Indeed, combining ERG and VEP methods have proven useful for mapping functional degeneration within the visual pathway in multiple sclerosis.^{17,18} Thus, ERG in conjunction with VEP may be sensitive to changes in brain function associated with CRNT.

OCT and ERG are emerging as useful surrogates for brain structure and function, respectively. As reviewed above, these ophthalmic measures have been used to track disease progression in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Furthermore, ophthalmic biomarkers are rapid, non-invasive, and inexpensive, making them ideal surrogates for neuroimaging measures that are more expensive and time-consuming. Thus, the clinical utility of ophthalmic biomarkers may improve the accessibility and throughput for evaluating neurodegeneration. It is therefore important to determine whether these markers may be useful for detecting CRNT.

Purpose of current review

The purpose of this review was to determine whether ophthalmic biomarkers such as OCT and ERG produce reliable changes that may be predictive of CRNT. To this end, the current review aimed to survey all published studies that included ophthalmic biomarkers in studies of cancer patients who received chemotherapy. To rule

out contributions for CNS disease, we did not consider CNS or retinal diseases.

Methods

Literature database search

A systematic literature review was conducted on June 2, 2019 in the PubMed database. Search terms consisted of Medical Subject Heading (MeSH) terms ("chemotherapy", "retina", "vision", "visual", "electroretinography", "optical coherence tomography"). A total of 3,488 unique published articles were produced from these search terms.

Inclusion and exclusion criteria

Articles were screened for studies that obtained objective ophthalmic biomarkers from adult cancer patients who were receiving or had received anti-neoplastic chemotherapy. Articles were excluded from review if they met any of the following criteria: (1) case reports or small ($n < 5$) studies; (2) patients less than 19 years of age; (3) studies comprising non-cancer patients; (4) studies comprising patients diagnosed with cancer of the CNS or retina; (5) studies comprising patients receiving hormone therapies; (6) non-human animal studies; (7) use of non-objective assessments of visual function or lack of objective biomarkers; and (8) not published in English. A total of six published articles met our inclusion criteria and were included for subsequent review (Figure 1).

Data extraction

All six articles meeting the inclusion criteria were evaluated for the purposes of this review (see Results). To provide an overview of all empirical findings, we created a summary table containing the following data elements: (1) cancer diagnosis; (2) chemotherapy agents; (3) study design; (4) assessment schedule; and (5) changes in OCT and ERG parameters.

Results

All six articles are summarised in Table 1. A total of 111 patients were treated for the following cancer

Figure 1. Selection process of studies.

Table 1. Review summary.

Cancer Type	Treatment	Design	Assessment Schedule	Outcome
[1] Ovarian (n = 13)	Cisplatin	Retrospective	Unknown time since treatment	↓ cone- and rod-mediated waveforms
[2] Germ Cell (n = 14)	Cisplatin	Retrospective	20 months post-treatment	↓ RNFL Thickness ↓ Macular Thickness ↑ cone a-wave latency ↓ cone b-wave amplitude
[3] Breast (n = 30)	Paclitaxel Only (n = 14) Paclitaxel + Doxorubicin (n = 16)	Prospective	Base, 3 cycles, 6 cycles, post-treatment	↑ b-wave latency (Paclitaxel) ↑ OP latency (Paclitaxel) ↓ OP amplitude (Paclitaxel)
[4] NSCLC (n = 15)	Cisplatin + Paclitaxel	Prospective	Base, 3-months, 6 cycles	↓ RNFL thickness
[5] Breast (n = 22)	Docetaxel (n = 23)	Prospective	Base, 4 cycles	↑ Macular Thickness
Oesophageal (n = 2)	Paclitaxel (n = 2)			
Ovarian (n = 1)				
[6] Colon (n = 13)	Bevacizumab	Prospective	Base, 1 cycle, 11 cycles	No change in macular or RNFL thickness
Breast (n = 2)				
Lung (n = 1)				
Rectal (n = 1)				

NSCLC = non-small cell lung cancer; RNFL = retinal nerve fibre layer; OP = oscillatory potential;

[1]³⁴; [2]³⁵; [3]³⁶; [4]³⁷; [5]³⁸; [6]³⁹

diagnoses: breast (n = 54); lung (n = 16); germ cell (n = 14); colon (n = 13); ovarian (n = 13); oesophageal (n = 2); and rectal (n = 1). Patients received the following chemotherapy agents: cisplatin (n = 27); paclitaxel (n = 16); cisplatin and doxorubicin (n = 15); cisplatin and paclitaxel (n = 15); docetaxel (n = 23); and bevacizumab (n = 17). Study designs

were both retrospective (n = 2) and prospective (n = 4). In general, these studies found evidence for chemotherapy-related alterations in both retinal structure and function. Each study is reviewed in detail below.

Wilding and colleagues retrospectively evaluated patients diagnosed with stage III/IV ovarian cancer

($n = 13$) who had previously received high-dose cisplatin therapy.³⁴ Patients had received cycles of 40 mg/m² cisplatin daily for five days every 28 days (mean cumulative dose: 642 ± 115 mg/m²). Patients who were previously untreated (46%) had also received cycles of 200 mg/m² cyclophosphamide every five days. Pattern VEP and flash ERG protocols were included as ophthalmic biomarkers. Abnormal waveforms were counted for cases that exceeded three standard deviations beyond unreported normative data. The authors reported 82% of patients showed a reduction in cone-mediated waveforms, and 55% of patients showed a reduction in rod-mediated waveforms. VEP amplitudes were reduced in 14% of patients. Of all patients showing abnormal cone-mediated waveforms, 67% showed reduced cone-mediated visual light thresholds, and 60% of all patients showed abnormal cone-mediated waveforms and visual light thresholds. There were several limitations to this study, including the retrospective design, a heterogeneous sample of patients who all received at least one non-cisplatin chemotherapy agent, and lack of information regarding time since last treatment.

Dulz and colleagues retrospectively evaluated patients diagnosed with germ cell cancer ($n = 14$) who had previously received cisplatin-based treatment.³⁵ Patients received an average cumulative cisplatin dose of 686 ± 295 mg/m², and were evaluated an average of 27.7 ± 21.1 months post-treatment. Information on cisplatin dosages per cycle or other previous treatments were not reported. Ophthalmic biomarkers included OCT of the macula and RNFL, flash ERG, and flicker ERG. Age-matched healthy controls ($n = 14$) underwent the same procedures. The authors reported that 79% of patients and 75% of eyes showed reduced RNFL thickness in one or more segments, which were primarily noted in the inferior and temporal quadrants. Significant reductions in macular thickness were also reported in the outer superior, temporal, and inferior macular regions. Higher cumulative cisplatin dosages were associated with reduced RNFL thickness. No other associations were found between OCT thickness parameters and either cumulative cisplatin dose or post-treatment time. Significant ERG findings were limited to reduced cone b-wave amplitudes, whereas cone a-wave amplitudes and cone-mediated flicker ERGs were indistinguishable from healthy controls. There

were several limitations to this study, including the retrospective design and a lack of details regarding previous treatments.

Scaioli and colleagues prospectively evaluated patients diagnosed with metastatic breast cancer ($n = 30$).³⁶ Patients were either scheduled to receive paclitaxel alone ($n = 14$; Group A) or paclitaxel and doxorubicin ($n = 16$; Group B). Patients in Group A were those who had previously received no more than two chemotherapy agents and had progressed within 12 months of their last chemotherapy; paclitaxel was administered three times per week at 200 or 225 mg/m² per dose for at least four cycles, where cumulative paclitaxel doses ranged from 950 to 2475 mg/m². Patients in Group B received paclitaxel at the same dosage and schedule as Group A, with a cumulative paclitaxel dose that ranged from 700 to 2800 mg/m², and doxorubicin (60 mg/m²) for no more than eight total cycles. Patient groups were compared with age-matched controls. Ophthalmic biomarkers included pattern VEP, flash ERG, flicker ERG, and OPs. Both groups completed study procedures prior to initiating treatment, after their third and sixth cycles, and after completing treatment. The authors reported significant differences between patient and control groups at baseline, though these findings may be attributable to cancer pathophysiology or other co-morbidities and are therefore outside the scope of this review. During treatment, Group A showed chemotherapy-related reductions in OP amplitude and increases in b-wave and OP latencies, whereas no changes were noted in a-wave, flicker ERG, or VEP parameters. No changes were noted in Group B in any measure. The authors noted changes in OP were positively correlated with changes in visual symptoms. This study was limited by the inclusion of metastatic patients with unknown CNS involvement and a patient group (A) that had previously received treatment.

Bakbak and colleagues prospectively evaluated patients diagnosed with non-small-cell lung carcinoma (NSCLC) patients ($n = 15$) who were scheduled to receive combination treatment with cisplatin (75 mg/m²) and paclitaxel (175 mg/m²) every three weeks for a maximum of six cycles.³⁷ No information was provided on cumulative dosages or number of completed cycles. Ophthalmic biomarkers included OCT RNFL and intraocular pressure (IOP) measurements. Study procedures were completed prior to

initiating treatment and three months after completing treatment. The authors reported significant reductions in RNFL thickness, as well as significant reductions in performance in automated visual perimetry. This study was limited by short-term follow-up, which may have limited the extent of neurotoxicity, and the lack of information on cumulative dosages, which may have provided insights into the relationship between chemotherapy dosage and the decline in RNFL thickness.

Chelala and colleagues prospectively evaluated any patient referred by an oncologist who was scheduled to receive taxane-based chemotherapy.³⁸ Enrolled patients included those who were diagnosed with breast ($n = 22$), oesophageal ($n = 2$), and ovarian ($n = 1$) cancers and had not previously received taxane-based chemotherapy. Patients received either docetaxel-based treatment ($n = 23$) or paclitaxel-based treatment ($n = 2$). Ophthalmic biomarkers were limited to OCT macular measurements. Study procedures were completed prior to initiating treatment and after completion of four treatment cycles. The authors reported a significant increase in macular thickness primarily in the superior parafoveal and temporal, superior, nasal, and inferior perifoveal regions. The authors attributed chemotherapy-related increases in macular thickness to cystoid macular oedema due to disruption of the blood-retinal barrier. This study was limited by the heterogeneous cancer population, lack of information on additional treatments in chemotherapy regimens, and a lack of information on RNFL thickness from OCT measurements.

Yildiz and colleagues prospectively evaluated patients diagnosed with colorectal ($n = 14$), lung ($n = 1$), or breast ($n = 2$) cancer who were scheduled to receive bevacizumab in combination with 5-fluorouracil, oxaliplatin, and irinotecan.³⁹ Bevacizumab was administered at either 5, 7.5, or 15 mg/kg per day once every two weeks for three to nine months. Patients received a median of 11 total treatment cycles (range: 7–18) for a median total dose of 5,585 mg (range: 2,800–16,200 mg). Ophthalmic biomarkers included OCT measurements of macular and RNFL thickness. Study procedures were completed prior to initiating treatment, after the first treatment cycle, and after completing treatment. The authors reported no significant changes in macular and RNFL

thickness, and no association between OCT thickness parameters and total bevacizumab dosage. This study was limited by the heterogeneous cancer population and a lack of information on additional treatments received.

Discussion

Overview of findings

The purpose of this review was to survey the literature for evidence of chemotherapy-related changes in retinal structure and function to determine whether ophthalmic biomarkers may be useful for tracking CRNT. We found that the literature in this area, while limited, generally converged on the same conclusions: cancer patients receiving chemotherapy show reduced retinal thickness and inner retinal function. Critically, however, conclusions made from these articles are limited by several issues, including study design and sample characteristics. Thus, further work is necessary to overcome the limitations of published work in this area.

Approximately 38% of the patients reviewed received cisplatin-based treatment.^{34,35,37} Patients generally showed reductions in RNFL thickness^{35,37} and reduced cone pathway function,^{34,35} with one study also reporting reduced rod pathway function.³⁴ These findings are consistent with clinically-relevant findings of cisplatin-induced retinopathy.^{40,41} To our knowledge, however, these are the only studies that have systematically evaluated retinal markers of cisplatin-induced retinopathy.

Approximately 63% of the patients reviewed received taxane-based treatment.^{36–38} Patients generally showed reduced RNFL thickness,³⁷ increased macular thickness,³⁸ and reduced inner retinal function of bipolar and amacrine cell populations.³⁶ We were unable to identify convergence between findings because each study used different ophthalmic measures. Previous reviews have identified ocular toxicities associated with taxane-based treatments,^{15,42} though taxane-induced retinopathy is not currently recognised as a clinically relevant outcome.

This review has highlighted preliminary empirical evidence suggesting chemotherapy leads to visual pathway degeneration. It remains unclear, however, whether chemotherapy-related visual pathway degeneration is related to, or shares

common pathophysiological mechanisms with, CRNT. Findings reviewed here must be further explored in future research to better understand the pathophysiological mechanisms of chemotherapy-related visual pathway degeneration, and further explore the relationship between CRNT and changes in retinal structure and function.

Opportunities for future research

Improvements in clinical study design will be necessary to carry the state of the science forward. Studies reviewed here were either retrospective^{34,35} or prospective with multiple cancer diagnoses^{38,39} and chemotherapy protocols.^{37,39} Future research will benefit by using prospective studies of patients with homogeneous cancer diagnoses. Furthermore, including multiple time points during and after treatment will improve the resolution of dose-dependent and long-term changes in retinal structure and function. Focusing on a single chemotherapy protocol, rather than multiple protocols with a common agent, will improve clinical relevance and directions for future research to isolate neurotoxic agents.

Ophthalmic measures have potential to be used as biomarkers of CRNT. To date, neuroimaging methodologies and neurocognitive assessments have primarily been used to study CRNT in the context of chemotherapy-related cognitive impairment.^{4–6} Critically, however, these studies do not account for possible contributions of visual pathway degeneration to changes in task-evoked brain activity and neurocognitive performance.¹⁴ Linking chemotherapy-related changes in retinal structure and function, brain structure and function, and neurocognitive function will improve the translational utility of ophthalmic measures to be used as biomarkers of CRNT while simultaneously controlling for visual pathway degeneration.

Animal studies will be critical for isolating the pathophysiological mechanisms of changes in retinal structure and function following treatment with specific chemotherapy agents. *In vitro* studies have begun evaluating molecular and cellular mechanisms of chemotherapy-induced retinal toxicity.^{43–46} Incorporating longitudinal *in vivo* OCT and ERG measurements into animal studies, as has been done with diabetic retinopathy,⁴⁷ will

improve translational links between animal and clinical research programmes.

Conclusions

CRNT is an emerging public health concern. Improving quality of life in post-chemotherapy cancer survivors will require developing research programmes aimed at detecting and preventing CRNT. The retina is a novel and accessible measure of brain structure and function, and may prove to be a valuable tool in detecting CRNT. This review demonstrated that this area of research is understudied. Nevertheless, preliminary evidence suggests chemotherapy may selectively impair visual pathway function. Future research will be valuable in better understanding the mechanisms of chemotherapy-related visual pathway degeneration and developing ophthalmic biomarkers of CRNT.

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Declaration of interest

The authors have no conflicts of interest to disclose.

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