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Evaluation of Retinal Toxicity in Pediatric Oncology Patients Receiving Platinum-Based Chemotherapy

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What is already known on this topic?

- *Platinum-based chemotherapies, particularly cisplatin, have been linked to ocular toxicities such as optic neuritis, papilledema, and retinal ischemia mostly reported in adults.*
- *Pediatric data are scarce and largely anecdotal; only a few case reports and small case series have evaluated retinal effects in children.*
- *Optical coherence tomography (OCT) and OCT angiography (OCTA) allow non-invasive detection of subclinical retinal and microvascular changes before visual symptoms emerge.*
- *Cumulative dose and route of administration (intra-arterial > intravenous) are thought to modulate the risk and severity of retinal toxicity.*

ABSTRACT

Objective: Improved survival among pediatric oncology patients has increased the burden of late treatment-related complications, including retinal toxicity, a recognized acute and chronic effect of platinum chemotherapy. This study aimed to characterize retinal toxicity associated with platinum agents and compare the toxicities of cisplatin and carboplatin.

Materials and Methods: Thirty-six pediatric patients (22 girls, 14 boys) who had completed platinum-based chemotherapy and were in remission were evaluated. Patients with pretreatment ocular disease or impaired renal function were excluded. Oncologic data and ophthalmologic findings including visual acuity, refractive errors, color vision, optical coherence tomography (OCT) (retinal nerve fiber layer thickness [RNFLT]; central foveal retinal thickness [CFRT]), and optical coherence tomography angiography (OCTA) (superficial capillary plexus [SCP]; deep capillary plexus [DCP]) vessel density were obtained retrospectively from medical records. Thirty-six age- and sex-matched healthy children without ocular or systemic disease served as controls.

Results: Seventy eyes from the patient group and 72 from controls were analyzed. Time since last chemotherapy was negatively correlated with left-eye CFRT. Higher cumulative cisplatin dose was associated with reduced CFRT and thinning of RNFLT in the nasal-superior quadrant, while carboplatin dose showed no significant effect.

Conclusion: Obvious retinal toxicity does not occur with platinum chemotherapy within the dosage range the patients received. The decrease in CFRT and RNFLT with a higher dose of cisplatin suggested that cisplatin may cause more retinal toxicity than carboplatin. The negative correlation between CFRT and duration since last chemotherapy suggests that RNFLT might get thinner over time; therefore, these patients need lifelong ophthalmologic follow-up.

Keywords: Carboplatin, cisplatin, OCT, OCTA, retinal toxicity, RNFLT

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INTRODUCTION

Improvements in treatment modalities and chemotherapy in recent years have resulted in a significant increase in the survival rates of pediatric oncology patients. Therefore, the number of cancer survivors who suffer from long-term side effects is increasing. Platinum-based chemotherapies (cisplatin, carboplatin) are used in patients with solid tumors such as neuroblastoma, germ cell tumors, osteosarcoma, retinoblastoma, hepatoblastoma, brain tumors (especially low-grade gliomas and medulloblastoma/embryonal tumors), and soft tissue sarcomas. The most common side effects of platinum derivatives are nephrotoxicity and neurotoxicity.[1] Studies on the visual side effects of these agents are much more limited.[2]

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What does this study add to this topic?

- *The first systematic OCT/OCTA study in a cohort of pediatric cancer survivors (n = 36) treated intravenously with platinum agents provided paired structural and perfusion metrics.*
- *Identifies a dose-dependent decline in central foveal retinal thickness (CFRT) and nasal-superior retinal nerve fiber layer thickness with cumulative cisplatin, whereas carboplatin shows no measurable effect, highlighting differential retinal vulnerability.*
- *Demonstrates a negative correlation between CFRT and time since chemotherapy, suggesting progressive thinning long after treatment completion.*

Retinal and macular pathologies have been reported with intra-arterial cisplatin.[3] Cases of unilateral papilledema, bilateral retrobulbar neuritis, and optic neuritis have been reported with high-dose cisplatin and carboplatin.[4-9] These findings support the possibility of retinal toxicity with platinum-based chemotherapies. Studies investigating the retinal toxicity of platinum-based chemotherapy in pediatric patients are scarce in the literature. Therefore, the aim was to evaluate retinal toxicity in remission or cured pediatric oncology patients treated with platinum-based chemotherapy.

MATERIALS AND METHODS

This was a retrospective case control study. It was conducted between July 2020 and January 2021 in the Department of Pediatric Oncology at Gazi University, Ankara, Türkiye. The study included 36 patients [22 girls, 14 boys; median age 12.5 (5-17) years] with various malignant tumors who were either survivors or in remission and had been treated with platinum-based chemotherapy. Patients with impaired renal function tests and a history of eye disease before treatment were excluded from the study. Eye examination data [visual acuity (VA), refractive errors, color vision, optical coherence tomography (OCT) and retinal nerve fiber layer thickness (RNFLT), optical coherence tomography angiography (OCTA)] performed during the follow-up of the patients were obtained retrospectively from their ophthalmology files. Of 58 screened patients, 36 met the inclusion criteria; 22 were excluded due to pretreatment ocular disease (n = 6), abnormal renal function tests (n = 4), insufficient ophthalmic records/poor-quality imaging (n = 7), or lack of remission at the time of assessment (n = 5). As 1 eye of 2 patients was prosthetic, a total of 70 eyes from 36 patients were included in the analysis. Additionally, the right eye OCTA measurements of 1 patient could not be obtained due to technical limitations. All patients received intravenous platinum-based regimens (cisplatin and/or carboplatin). The 2 retinoblastoma patients had unilateral disease and received systemic intravenous therapy only; no selective intra-arterial or intravitreal administration was performed. The age and stage at diagnosis, pathology, chemotherapy protocol with cumulative carboplatin and cisplatin doses (cisplatin 55-600 mg/m^2 and carboplatin 600-8525 mg/m^2), and the time elapsed after the last chemotherapy cycle were retrospectively obtained from the records. No predefined toxicity cutoff was used due to the observational nature of the study.

As the control group, 36 pediatric patients who were examined for any reason in the ophthalmology department, with no known history of acute and chronic diseases and no known eye disorders, and who were suitable for the patient group in terms of age and sex were selected. Seventy-two eyes of these 36 patients were included in the study. The visual data of these patients were recorded retrospectively from their files.

Evaluation Methods Used in the Study

The Snellen chart, the autorefractometer, and the Ishihara test are used for VA measurement, refractive errors detection, and color vision evaluation, respectively.

Optical Coherence Tomography

Optical coherence tomography can provide data on peripapillary RNFLT and macular thicknesses and generate macular maps with segmental thicknesses and volumes.[10] Optical coherence tomography allows non-contact, non-invasive imaging of the anterior segment as well as visualization of the morphological features of the human retina, including the fovea and optic disc.[11]

The SD-OCT (Spectralis®, Heidelberg Engineering, Heidelberg, Germany) device was used for the measurements. With this device, the central foveal retinal thickness of the macula (CFRT), as well as global (G), temporal (T), temporal superior (TS), nasal superior (NS), nasal (N), nasal inferior (NI), nerve fiber thicknesses of the temporal inferior (TI) quadrants can be determined in microns. OCT assessments were reported using the device's built-in normative database with automatic color coding (green: within normal limits; yellow: borderline; red: outside normal limits). Because the color scale in the device is derived from an adult normative database, pediatric normality was interpreted against an age/sex-matched control group. In recent years, OCT has become the gold standard method for detecting glaucoma damage, as it simultaneously demonstrates RNFLT, macular ganglion cell, and optic nerve head changes with high reproducibility and reliability.[12-14] Representative OCT images from a platinum-treated patient in remission (Figure 1A) and an age- and sex-matched control (Figure 1B) illustrate preserved RNFLT values.

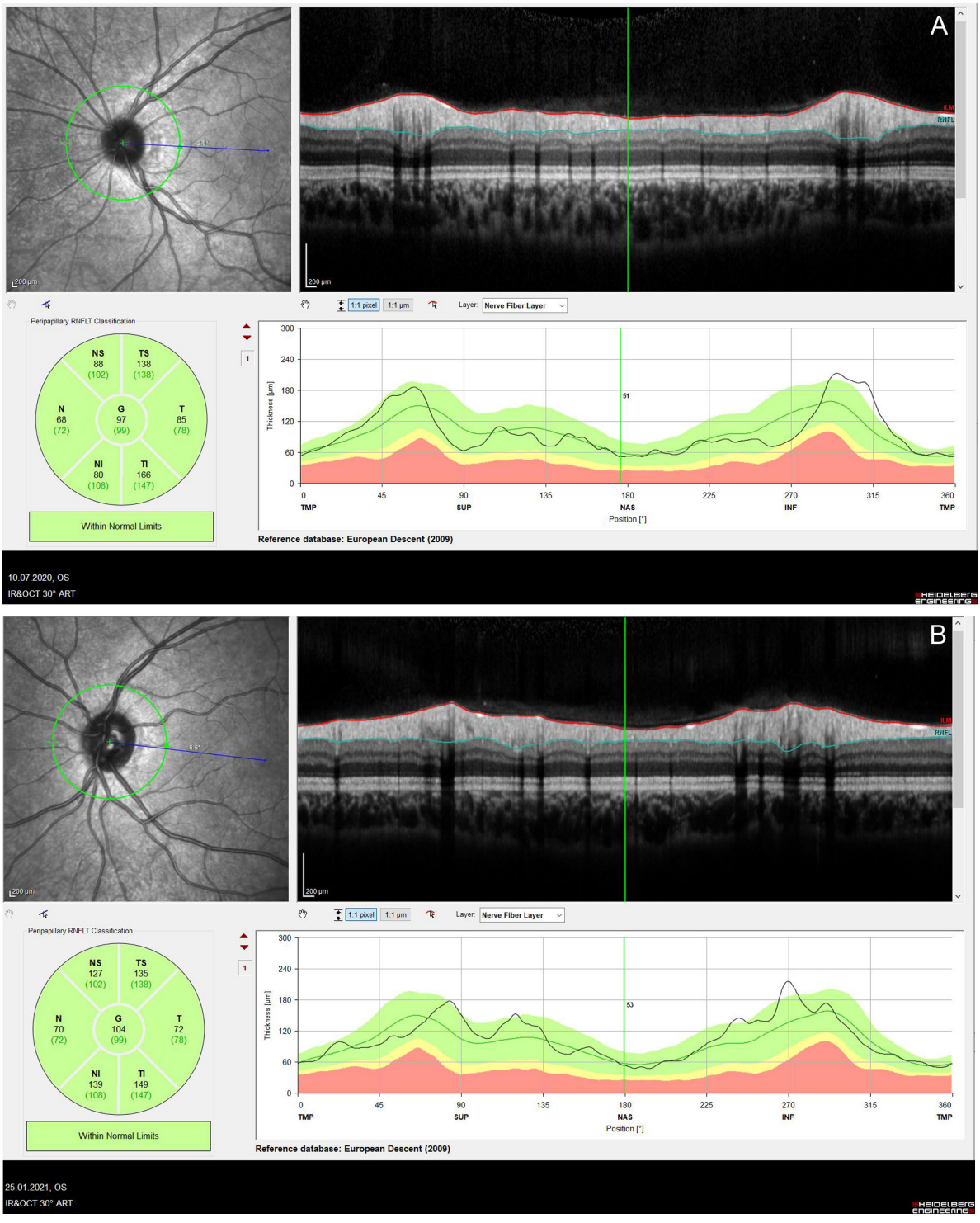

Figure 1. A: OCT image of the left eye from a 13-year-old female pediatric patient with germ cell tumor in remission. B: OCT image of the left eye from an age- and sex-matched healthy control.

Optical Coherence Tomography Angiography

Optical coherence tomography angiography is an imaging method to provide detailed visualization of the perfusion of the vascular networks in the eye. Optical coherence tomography angiography is non-invasive, efficient in terms of time management, and allows 3-dimensional examination of retinal vascular structures.[15] A revascularization map is created by using blood-filled vessels in the retina and choroid.[16]

Optical coherence tomography angiography imaging was performed with a commercial OCTA system (AngioVue, RTVue XR, Angiovue, Optovue, Inc. Fremont, CA, USA). Superficial

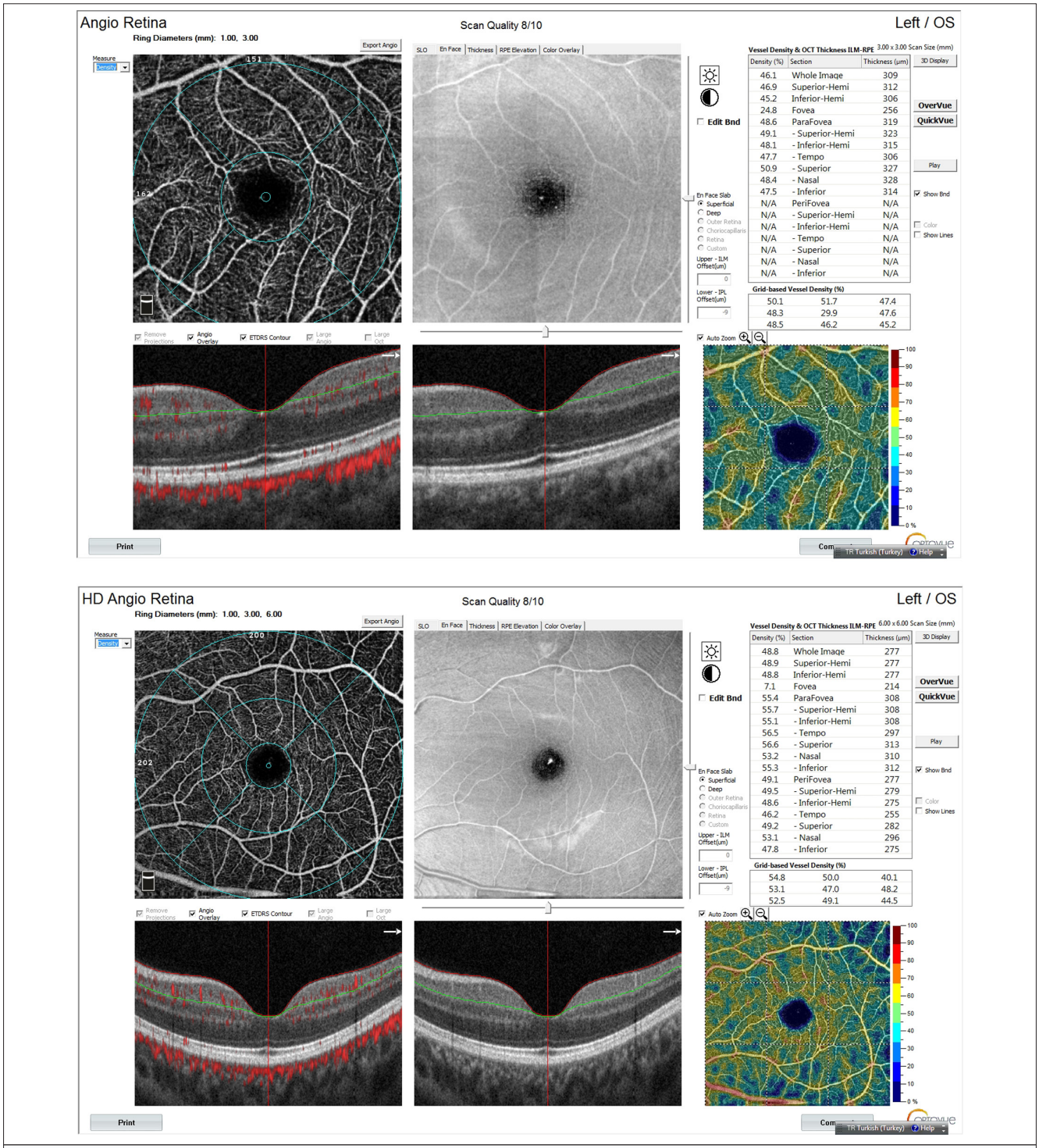

Figure 2. A: OCTA image of the left eye from a 13-year-old female patient with germ cell tumor in remission. B: OCTA image of the left eye from an age- and sex-matched healthy contro.

and deep-layer retina segmentation was done automatically with the device's software. Given the limited pediatric device norms for OCTA, vessel density values were interpreted relative to age- and sex-matched controls. Representative OCTA images from a platinum-treated patient in remission (Figure 2A) and an age- and sex-matched control (Figure 2B) are shown; color perfusion maps are provided for illustration only.

.Analysis of Data

Analyses were performed using the Statistical Package for the Social Sciences, version 22.0 (IBM Corp.; Armonk, NY, USA).

Table 1. The Characteristics of the Patients

	Patients n = 36, n (%)	Controls n = 36, n (%)	*P*
Sex			
Female	22 (61.1)	26 (72.2)	**.317**
Male	14 (38.9)	10 (27.8)	
Age at diagnosis	12.5 (5;16)	11 (6;14)	.320
Diagnosis		**Chemotherapy**	
Neuroblastoma	9 (25)	Cisplatin/carboplatin/etoposide/cyclophosphamide/doxorubicin	
Germ cell tumor	9 (25)	BEP*, PVB§, VAC†	
Astrocytoma	3 (8.3)	Carboplatin/vincristine	
Osteosarcoma	3 (8.3)	EURAMOS‡ protocol	
Retinoblastoma	2 (5.6)	Carboplatin/vincristine/etoposide	
Hepatoblastoma	2 (5.6)	Cisplatin/carboplatin/vincristine/cyclophosphamide	
Medulloblastoma	2 (5.6)	Cisplatin/vincristine/cyclophosphamide	
Synovial Sarcoma	2 (5.6)	Carboplatin/vincristine/doxorubicin	
Rhabdomyosarcoma	1 (2.8)	Carboplatin/VAC	
Nasopharyngeal carcinoma	1 (2.8)	Cisplatin	
Lymphoma	1 (2.8)	Carboplatin/CHOP#	
Wilms	1 (2.8)	Carboplatin/vincristine/doxorubicin	

*BEP, bleomycin, etoposide, cisplatin.
§PVB, cisplatin, vincristine, bleomycin.
†VAC, vincristine, actinomycin D, cyclophosphamide.
‡EURAMOS, European and American Osteosarcoma Studies.
#CHOP, cyclophosphamide-doxorubicin-vincristine-prednisolone.

Continuous variables were summarized as median (IQR) or median (minimum–maximum), as appropriate; categorical variables as n (%).

Since the sample consisted of 36 patients and 36 age- and sex-matched controls, all comparison analyses were performed with nonparametric tests. The Mann–Whitney *U*-test was used to analyze 2-category variables and numerical variables, and the Spearman correlation test was used to analyze numerical variables with each other. The strength of Spearman correlations was interpreted as follows: <0.25 very weak, 0.26-0.49 weak, 0.50-0.69 moderate, 0.70-0.89 high, and 0.90-1.00 very high. $P < .05$ was considered statistically significant.

Ethical Aspect of Research

Written study permission dated July 6, 2020 and numbered 418 was obtained from Gazi University's Clinical Research Ethical Committee for this study. Written informed consent was obtained from all participants' legal guardians.

Table 2. Comparison of Visual Acuity and Refractive Errors of the Case and Control Groups

		Case	Control	*P*
		Median (min; max)	Median (min; max)	
Visual acuity	Right	1.00 (0.5; 1.00)	1.00 (0.2; 1.00)	.758
	Left	1.00 (0.4; 1.00)	1.00 (0.3; 1.00)	.435
Spherical (D)	Right	0.25 (0.0; 5.5)	0.62 (0.0; 8.8)	.519
	Left	0.50 (0.0; 5.5)	0.50 (0.0; 7.7)	.811
Cylindrical (D)	Right	0.50 (0.0; 2.0)	0.40 (0.0; 2.0)	.763
	Left	0.50 (0.0; 2.7)	0.50 (0.0; 3.2)	.465

Data are median unless otherwise indicated.
D, diopter.

RESULTS

Among 36 patients, diagnoses were neuroblastoma (25%), germ cell tumor (25%), astrocytoma (8.3%), osteosarcoma (8.3%), retinoblastoma (5.6%; unilateral), hepatoblastoma (5.6%), medulloblastoma (5.6%), synovial sarcoma (5.6%), rhabdomyosarcoma (2.8%), nasopharyngeal carcinoma (2.8%), lymphoma (2.8%), and Wilms tumor (2.8%). All patients received intravenous platinum-based combination regimens, most commonly cisplatin/carboplatin in various combinations with etoposide, vincristine, cyclophosphamide, and/or doxorubicin. Regimen backbones included bleomycin, etoposide, cisplatin/cisplatin, vincristine, bleomycin/vincristine, actinomycin D, cyclophosphamide-for germ cell tumors, European and American Osteosarcoma Studies for osteosarcoma, and cyclophosphamide-doxorubicin-vincristine-prednisolone for lymphoma; diagnostic and treatment details are summarized in Table 1. Twelve (33.3%) of the 36 patients included in the study were treated with only carboplatin-based chemotherapy, 19 (52.3%) with only cisplatin-based chemotherapy, and 5 (13.9%) with both carboplatin and cisplatin-based chemotherapy. Cumulative cisplatin and carboplatin doses were 400 mg/m^2 (range 55-600) and 2800 mg/m^2 (range 600-8525), respectively. Renal function tests were within normal limits for all patients.

Color vision was normal in all case and control groups. There were no between group differences in VA or refractive error for either eye (right VA $P = .758$, left VA $P = .435$; Table 2). The 2 patients with retinoblastoma had unilateral disease, and only the unaffected fellow eye was included in the analysis; in both patients, VA was preserved, and OCT findings were normal in the analyzed eye. The 2 patients with medulloblastoma had no documented central nervous system lesions (including optic pathway disease or brain parenchymal lesions) at diagnosis or

Table 3. Retinal Nerve Fiber Layer Thickness Data of Case and Control Groups

		Case	Control	*P*
		Median (min; max)	Median (min; max)	
Central foveal retinal thickness (µm)	Right	257.0 (226; 291)	263.0 (225; 337)	.421
	Left	258.0 (220; 327)	258.5 (225; 310)	.674
RNF* Central thickness (µm)	Right	99.0 (37; 126)	100.0 (49; 119)	.621
	Left	95.0 (39; 115)	98.5 (72; 116)	.101
RNF Temporal thickness (µm)	Right	74.0 (34; 91)	76.0 (37; 115)	.357
	Left	71.0 (27; 251)	72.0 (55; 119)	.292
RNF Temporal superior thickness (µm)	Right	136.0 (52; 172)	145.0 (100; 177)	.395
	Left	133.0 (45; 175)	136.5 (89; 162)	.465
RNF Nasal superior thickness (µm)	Right	100.0 (35; 149)	111.5 (43; 162)	.166
	Left	116.0 (35; 151)	118.5 (89; 174)	.16
RNF Nasal thickness (µm)	Right	79.0 (28; 156)	71.0 (31; 127)	.216
	Left	70.0 (8; 102)	68.5 (39; 101)	.959
RNF Nasal inferior thickness (µm)	Right	103.0 (38; 148)	102.5 (36; 145)	.895
	Left	100.0 (27; 156)	108.0 (67; 151)	.139
RNF Temporal inferior thickness (µm)	Right	144.0 (40; 175)	144.5 (49.2; 185)	.836
	Left	140.0 (46; 173)	145.5 (66; 170)	.577

*RNF, retinal nerve fiber.

during follow-up. Across the entire cohort, no peri-treatment or posttreatment neuropathic findings (e.g., distal paresthesia, gait disturbance) were documented in the medical records.

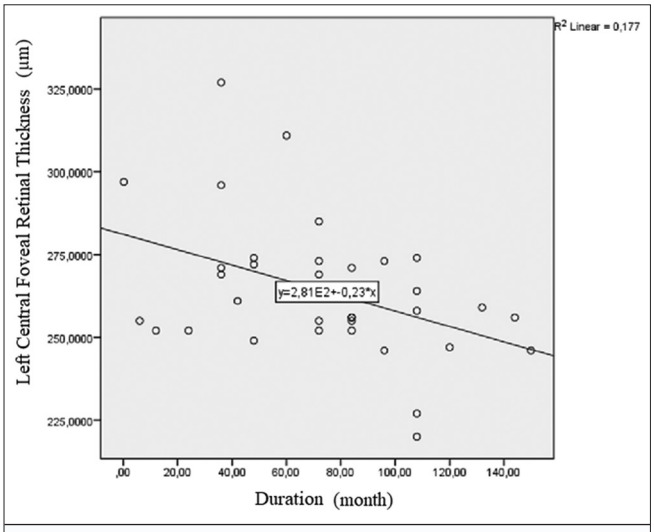

Figure 3. Correlation between duration after cessation of chemotherapy and mean central foveal retinal thickness of the left eye.

The OCT data of the patients during their oncological follow-up and the OCT data of the control group are summarized in Table 3. A comparison of OCT data between groups was evaluated using the Mann–Whitney *U*-test, and no difference was found. Control subjects had normal ocular examinations. OCT outputs were predominantly green, and, acknowledging that the color codes are adult based, case control comparisons were used for pediatric interpretation.

The time since the last platinum-based chemotherapy was a median of 72 months (range 11-150). The correlation between

Table 4. Comparison of Optical coherence tomography angiography Data of Case and Control Groups

		Case			Control			*P*
		Min	Max	Median	Min	Max	Median	
Vascular density of the superficial capillary plexus (%)								
Entire retina	Right	38.8	54.4	48.7	39.2	52.6	49	.609
	Left	32.5	53.1	47	33.7	52.3	48	.101
Superior	Right	38.7	54	48.4	42.4	53	49.4	.287
	Left	31.9	53	47.8	32.7	52.1	47.6	.245
Inferior	Right	38.9	54.8	49.1	36	59.9	49.3	.63
	Left	20	53.2	46.8	34.1	53.2	47.8	.122
Fovea	Right	6.2	35.6	19.5	8.2	28.4	17.4	.35
	Left	5.7	55.1	19	7.1	30.4	18.5	.95
Parafovea	Right	42.3	56.7	51.9	41.7	56.2	52.6	.259
	Left	0.17	57.4	50.1	36.3	56.1	50.9	.111
Vascular density of the deep capillary plexus (%)								
Entire retina	Right	44.5	59.6	52.9	40.7	59.4	52.8	1
	Left	34.3	57	51.7	33.8	57.6	53	.089
Superior	Right	45.3	59.7	53.1	40.1	59.5	53.3	.869
	Left	34.4	57.3	52.3	32.6	58.6	52.8	.127
Inferior	Right	42.7	58.4	52.4	38.9	59.6	52.7	.902
	Left	34.3	57.7	51.4	35	57.8	53.5	.054
Fovea	Right	17.4	50	34.7	19.6	45.2	33.7	.492
	Left	18.1	49.1	36	23.8	45.4	34.8	.931
Parafovea	Right	49.4	61.5	55.2	47.7	61.7	56	.972
	Left	38.3	58.4	54.6	42.4	60.1	55.7	.173

Table 5. Correlation of Cumulative Cisplatin and Cumulative Carboplatin Doses with Optical Coherence Tomography Data

	Central Foveal Retinal Thickness (μm)			
	Right		Left	
	S	*P*	S	*P*
Cumulative cisplatin dose (mg/m^2)	−0.263	.276	−0.458	**.049***
Cumulative carboplatin dose (mg/m^2)	0.600	.051	−0.261	.386

S, Spearman correlation coefficient.
*P < .05.

the time elapsed after the cessation of chemotherapy and the left-eye CFRT values was evaluated with the Spearman correlation test and summarized in Figure 3. A statistically significant (P = .032) weak negative (−0.369) correlation existed between them. No correlation was found in the right eye (P = .454).

When the OCTA and superficial capillary plexus (SCP) vascular density and deep capillary plexus (DCP) vascular density percentages of the case and control groups were measured for both eyes and retinal quadrants (whole retina, superior half, inferior half, fovea, parafovea) and compared with the Mann–Whitney *U*-test, no difference was found. The findings are given in Table 4. Optical coherence tomography angiography vessel densities were reported relative to a control group rather than pediatric normative thresholds; color maps were not used for analytical decisions.

The correlation of the cumulative doses of carboplatin and cisplatin with the OCT data (CFRT) was evaluated with the Spearman correlation test and summarized in Table 5. There was no correlation between CFRT and cumulative carboplatin dose in the right and left eyes (P = .051, P = .386). Central foveal retinal thickness had a statistically significant (P = .049) but weak (−0.458) negative correlation with cumulative cisplatin dose in the left eyes. No correlation was found in the right eye (P = .276).

The correlation between the cumulative cisplatin and carboplatin dose and the central, T, TS, NS, N, NI, and TI RNFLT values of both eyes was evaluated by the Spearman correlation test and summarized in Table 6. There was no correlation between the cumulative carboplatin dose and the RNFLT values of any quadrant of the right and left eyes. Cumulative cisplatin dose showed a statistically significant (P = .040) but weak (−0.475) negative correlation with nasal-superior RNFLT (Table 6). There was no correlation between cumulative cisplatin dose and RNFLT in other quadrants.

DISCUSSION

Platinum compounds are widely used in the treatment of pediatric tumors. Cisplatin and carboplatin have a similar pharmacokinetic profile and mechanism of action, but differences in chemical structures are responsible for different antitumor activities and toxicities.[17]

Despite the presence of the blood-retina barrier, the retina is vulnerable to the toxic effects of systemic drugs that cause

Table 6. Correlation of Cumulative Cisplatin and Carboplatin Doses and Retinal Nerve Fiber Layer Thickness

RNFLT			Cisplatin Cumulative Dose (mg/m^2)	Carboplatin Cumulative Dose (mg/m^2)
Central (μm)	Right	S	−0.367	0.300
		P	.122	.370
	Left	S	−0.256	0.066
		P	.290	.846
Temporal (μm)	Right	S	−0.081	0.263
		P	.743	.435
	Left	S	0.182	0.041
		P	.456	.905
Temporal superior (μm)	Right	S	−0.184	0.223
		P	.450	.509
	Left	S	0.015	0.023
		P	.950	.947
Nasal superior (μm)	Right	S	−0.154	0.428
		P	.528	.189
	Left	S	−0.475	0.164
		P	**.040***	.629
Nasal (μm)	Right	S	−0.375	0.575
		P	.114	.064
	Left	S	−0.101	−0.011
		P	.681	.973
Nasal inferior (μm)	Right	S	−0.319	−0.144
		P	.183	.673
	Left	S	−0.437	−0.223
		P	.061	.509
Temporal inferior (μm)	Right	S	−0.043	0.386
		P	.862	.261
	Left	S	0.065	0.164
		P	.792	.630

RNFLT, retinal nerve fiber layer thickness; S, Spearman correlation coefficient.
*P < .05

dysfunction and degeneration.[18] Ocular side effects related to platinum compounds are rare and have been reported generally in adult patients.[3–5, 8, 9, 19, 20] It is known to be much rarer in children.[2,7] Ocular toxicity has been reported more frequently with exposure to cisplatin than carboplatin.[2, 3, 10, 19, 21]

Impaired vision is an uncommon form of neurotoxicity due to cisplatin.[10] Retinal toxicity has been pointed out as a rare condition in a few case reports, although the underlying mechanism is not precise yet.[2,10,22] Retinal toxicity can present with loss of vision, blurred vision, double vision, altered color perception, and nystagmus.[2,5,21–24] Since retinal toxicity is dose-dependent, higher cumulative cisplatin doses cause more severe retinal toxicity.[21] In a study conducted by Wilding et al[21] in 1985, 13 adult female patients with ovarian cancer and progressive worsening visual complaints were evaluated for possible cisplatin-induced ocular toxicity. Among all patients who received high-dose cisplatin, blurred vision, impaired color vision, and cone dysfunction were reported. Compared to the current sample, these patients received higher cumulative doses of cisplatin, which suggested that these patients could be asymptomatic due to lower cumulative cisplatin doses.

Caraceni et al[25] reported a case in 2009 in which peripheral neuropathy was observed in a woman who received a high cumulative dose of cisplatin for ovarian cancer. Because of the peripheral neuropathy, cisplatin treatment was replaced with a high cumulative dose of carboplatin. It was observed that the patient had optic neuritis after those treatments, and it was thought that optic neuritis might be the result of carboplatin, cisplatin, or both treatments; however, since the delayed optic neuritis with intra-arterial cisplatin administration has been shown by other studies, it was thought to be more likely to be caused by cisplatin.[25] In this study, no patients had optic neuritis.

The presence of retinal or renal disease is also significant for retinal toxicity.[26] Hilliard et al[2] reported a case in 1997 in which a 4-year-old girl received cisplatin due to a germ cell tumor, and after her treatment, she had retinal toxicity documented by visual evoked response and electroretinogram. The patient's serum creatinine level was found to be normal before, during, and after chemotherapy, but was elevated at the beginning of the symptoms.[2] The second case was a 7-year-old girl with hepatoblastoma, and all renal functions were found to be normal before treatment. After the treatment with a regimen containing cisplatin, the patient's serum creatinine level increased. One week after treatment, complaints of blurred vision and seeing red objects as blue began.[2] Since renal clearance has an important role in cisplatin elimination, the authors speculated that retinal toxicity was due to decreased renal clearance of unbound platinum. The cases in this study did not have any visual complaints, and the anterior and posterior segment examinations of all patients were observed to be normal. In addition, all kidney function tests, including creatinine clearances, were within normal limits.

Orbital inflammation, optical neuropathy, papilledema, retinal detachment, and ocular and orbital toxicities are shown after intracarotid carboplatin and cisplatin treatments.[5,27] Therefore, intracarotid applications for both cisplatin and carboplatin are being avoided.[28] In light of these studies, it was observed that acute and severe retinal toxicity developed in intravitreal, intra-arterial, and intracarotid treatments. The patients all received platinum-based chemotherapy only intravenously; no other methods of administration were used.

Refractive errors are one of the leading causes of visual impairment worldwide.[29] In this study, it was observed that there was no significant difference between the patient and control groups in terms of refractive errors. It is believed that the high overall prevalence of refractive errors led to no difference between the patient group and the control group, and VA did not decrease with the platinum-based chemotherapy doses used in the patients.

Lately, OCT has become the gold standard method to determine glaucoma since it repeatedly and reliably shows RNFLT, macular ganglion cells, and changes in the optic nerve.[12–14] Kuang et al[30] showed that according to RNFLT measurements, retinal damage caused by glaucoma can be detected 5 years before visual field deficits occur. When the case and control groups were compared in this study, no statistically significant difference was found between the CFRT and 7-segment RNFLT values. Therefore, it is concluded that the retina is not affected by these medications.

The most important risk factor of retinal toxicity is being exposed to higher chemotherapy doses for a longer duration.[26] In this study, it was observed that the median CFRT in the left eye was negatively correlated with the time elapsed since the cessation of chemotherapy. No significant correlation was found in the right eye. Despite these discrepancies, they suggest that retinal thickness values may decrease as time elapses after platinum-based chemotherapy and that patients should be monitored for lifelong visual functions.

Along with providing evaluation in both structure and blood flow, OCTA allows the localization of the pathology.[31] In a study conducted by Sioufi et al[32] in 2019 with children who received cisplatin, there was no statistically significant difference between groups in VA and OCT data. In the OCTA data, there was no statistically significant difference between the groups in the SCP of the whole area; however, a statistically significant difference was found in all field DCP measurements between the patient group (48%) and the control group (52%) ($P = .026$). The authors suggested that since DCP is the region most prone to endothelial damage in the retina, retinal toxicity caused by chemotherapy can only be revealed with OCTA in the subclinical period.[32] However, this study did not find any statistically significant difference in the OCTA data. This may be related to the difference in the number of cases and the doses of platinum-based chemotherapy used.

Many studies have reported the importance of RNFLT determination for the early diagnosis and treatment of conditions involving the optic nerve, such as glaucoma and optic neuritis.[33] Optical coherence tomography can reveal changes in the RNFLT before any visual field defects occur. There are studies reporting that RNFLT decreased after treatment with cisplatin.[10,34] After treatment with carboplatin, it was seen in the literature that there were vision-related symptoms, mainly reported on a case-by-case basis, but no study was found showing a decrease in RNFLT.

In this study, the asymmetric involvement affecting the left eye, specifically, the reduction in median CFRT and the thinning of RNFLT in the nasal-superior quadrant of the left eye, cannot be convincingly ascribed to a specific biological mechanism. These observations are more plausibly explained by the small sample size, inherent interocular variability, measurement or segmentation variability, and the potential for type 1 error due to multiple comparisons. Accordingly, the findings should be interpreted with caution. Verification of laterality patterns will require larger, prospective studies in which potential confounders, such as ocular dominance, axial length, optic disc morphology, and scan centration, are standardized.

Experimental studies conducted by Yang et al[35] reported the potential toxic effect of cisplatin-based chemotherapy on retinal structures. In a study by Bakbak et al[34] 2014, it was shown that in lung cancer patients treated with cisplatin and paclitaxel, the mean RNFLT decreased 3 months after cessation of treatment. In this study, pretreatment and posttreatment RNFLT values could not be compared since RNFLT values before treatment started were unknown.

Cisplatin induced retinal toxicity is likely to involve multifactorial, interconnected mechanisms, which have been increasingly

elucidated in recent years. Updated mechanistic reviews highlight that oxidative stress via excessive production of reactive oxygen species and depletion of intrinsic antioxidants such as glutathione, superoxide dismutase, and catalase plays a key role in neuroretinal damage and endothelial cell injury.[36,37] This oxidative burden triggers mitochondrial dysfunction, impairing energy production in retinal ganglion cells, predisposing them to apoptosis.[38] Additionally, inflammation and DNA damage, including adduct formation, activate apoptotic pathways in retinal cells and vascular endothelium, further exacerbating tissue injury.[36] Disruption of the blood retinal barrier through endothelial toxicity can precipitate micro ischemia, subclinical edema, and structural thinning detectable via OCT and OCTA.[39,40]

Experimental data in animal models (e.g., cisplatin-treated neonatal rats) also support these mechanisms, demonstrating retinal ganglion cell death, vascular rarefaction, and retinal pigment epithelium alterations.[41] Taken together, these pathways may synergistically contribute to subclinical retinal thinning in pediatric patients, particularly with higher cumulative doses of cisplatin.

This cohort reflects real-world oncology practice in which most children receive combination chemotherapy. In the literature, ocular toxicities attributed to vincristine and cyclophosphamide are predominantly case-based, frequently arising within multi-agent regimens; thus, delineating a drug-specific retinal effect is inherently difficult. Reports with vincristine largely concern optic neuropathy or central (cortical) involvement, whereas consistent, isolated retinal toxicity in humans is limited.[42-44] For cyclophosphamide, ischemic retinopathy or cystoid macular edema has been described in case reports, often alongside taxanes or other agents.[45,46]

In addition, concomitant voriconazole use during intensive chemotherapy has been associated with treatment phase, typically reversible visual phenomena and electroretinographic chan ges;[39,44,47] because these patients were assessed in remission, any persistent retinal contribution from voriconazole is likely limited. Overall, overt, persistent platinum-related retinal toxicity was not detected; any dose–effect signals were weak and should be interpreted cautiously given these potential confounders.

Prospective studies with pretreatment baselines, standardized co-medication capture, and adequate power for agent stratified analyses are needed; this small, OCT+OCTA cohort underscores this and warrants confirmation in larger samples.

In conclusion, this study aimed to predict retinal toxicity, which is one of the important side effects of platinum group drugs, and to evaluate retinal toxicity in pediatric oncology patients. It was shown by these findings that, with the platinum-based chemotherapy doses used, significant retinal toxicity did not occur in these patients. However, with increasing cumulative doses, the decrease in the median CFRT value in the left eye and RNFLT detected in 1 segment of the left eye can be the early signs of ocular toxicity and indicate that care should be taken, especially in patients receiving high cumulative dose platinum-based chemotherapy, and it is important to monitor these patients for long-term ocular toxicity.

Limitations

This study is limited by its retrospective design, relatively small sample size, and lack of pretreatment ophthalmologic data. One major limitation is the absence of pretreatment ophthalmologic evaluations, which precludes the ability to differentiate pre-existing retinal changes from chemotherapy-induced damage. Additionally, the concurrent use of multiple chemotherapeutic agents makes it difficult to isolate the toxic effect of platinum compounds. Analyzing each eye separately may introduce intrasubject correlation and weaken the assumption of statistical independence; however, this approach was adopted to preserve data granularity and to detect eye-specific subclinical effects, and this risk was mitigated, to the extent possible, through the use of nonparametric methods. Despite these limitations, this study provides valuable insight into the potential retinal effects of cisplatin and carboplatin in pediatric patients.

Evidence linking vincristine and cyclophosphamide to ocular toxicity in children is largely case-based, commonly in multi-agent contexts, which introduces confounding by co-exposures. Moreover, voriconazole-related visual effects are typically transient during active therapy; given the remission assessments, persistent retinal contributions from such medications may be minimal, yet cannot be fully excluded.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

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