Original Article

Outcomes of neonatal retinoblastoma in pre-chemotherapy and chemotherapy eras

David A Camp[1], Lauren A Dalvin[1,2], Rachel Schwendeman[1], Li-Anne S Lim[1], Carol L Shields[1]

Purpose: To quantify outcomes for neonatal retinoblastoma patients treated during the pre-chemotherapy (1980–1994) and chemotherapy (1995–2018) eras. **Methods:** Retrospective review of retinoblastoma patients diagnosed within the first 28 days of life between 1/1/1980 and 11/30/2018. Student's *t*-test, Chi-square, and Fisher's exact test were performed to compare treatments and outcomes by era. **Results:** There were 68 patients with neonatal retinoblastoma (12% unilateral and 88% bilateral). According to era (pre-chemotherapy vs. chemotherapy), the number of treated patients was 26 (38%) vs. 42 (62%). Primary treatment was external beam radiotherapy (50% vs. 1%, $P < 0.001$), plaque radiotherapy (17% vs. 0%, $P < 0.001$), focal treatment (transpupillary thermotherapy or cryotherapy) only (21% vs. 14%, $P = 0.33$), intravenous chemotherapy (0% vs. 81%, $P < 0.001$), enucleation (10% vs. 4%, $P = 0.26$), or exenteration (2% vs. 0%, $P = 0.37$). Outcomes included tumor control (79% vs. 94%, $P = 0.02$), globe salvage (75% vs. 91%, $P = 0.02$), final gross visual acuity for salvaged eyes 20/200 or better (66% vs. 89%, $P < 0.01$), and death (19% vs. 0%, $P < 0.01$). **Conclusion:** Chemotherapy advancements for neonatal retinoblastoma have improved tumor control, globe salvage, visual acuity, and patient survival.

Key words: Cancer, chemotherapy, eye, intra-arterial, intravenous, intravitreal, neonatal, retinoblastoma

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_634_19

Quick Response Code:

Advancements in chemotherapy have revolutionized retinoblastoma management in recent decades.[1-25] In the 1990s, the introduction of intravenous chemotherapy (IVC) improved clinical outcomes and reduced the need for enucleation, while avoiding external beam radiotherapy (EBRT) and associated second cancers.[1-8] In a study of 249 consecutive eyes, IVC achieved globe salvage in 100% of group A, 93% of group B, 90% of group C, 47% of group D, and 25% of group E eyes.[6] In the 2000s, intra-arterial chemotherapy (IAC) further improved globe salvage rates for advanced eyes, with low risk for systemic side effects.[9-15] In a 5-year experience study of 70 consecutive eyes, IAC achieved globe salvage in 100% of group B, 100% of group C, 94% of group D, and 36% of group E eyes.[12] More recently, in the 2010s, intravitreal chemotherapy (IVitC) improved globe salvage in eyes with refractory or recurrent vitreous seeds.[16-22] In a study of 40 consecutive eyes with viable vitreous seeding treated with IVitC, complete vitreous seed resolution was found in 100% of eyes and globe salvage was achieved in 88% of eyes.[19]

While retinoblastoma outcomes have been previously explored by treatment era, studies have not specifically analyzed how these treatment advancements have impacted the youngest patient cohort with retinoblastoma, that is, the neonatal patients. Up to 10% of all retinoblastoma in developed countries is diagnosed in the neonatal period (within the first 28 days of life).[26] Patients with neonatal retinoblastoma have a unique set of characteristics that complicate management, including greater frequency of family history of retinoblastoma, bilateral disease, multiple tumors, and macular involvement.[26-29] One report[5] has suggested that patients are less likely to respond to IVC if younger than 2 months, and most clinicians agree that neonates cannot receive IAC using current techniques due to the risks of catheterizing small arteries.[30] Additionally, bilateral or familial retinoblastoma carries risk for developing trilateral retinoblastoma and second malignant neoplasms.[31-35] Given unique disease characteristics and treatment limitations, it is important to separately investigate treatment outcomes for neonatal retinoblastoma. Herein, we compare treatment outcomes for neonatal retinoblastoma in the pre-chemotherapy (1980–1994) and chemotherapy (1995–2018) eras.

Methods

Medical records were retrospectively reviewed to identify retinoblastoma patients at a single center from January 1, 1980 through November 30, 2018. Patients diagnosed with retinoblastoma within the first 28 days of life were included. Institutional Review Board approval was obtained. This study is in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and adheres to the tenets of the Declaration of Helsinki.

[1]Ocular Oncology Service, Wills Eye Hospital, Philadelphia, PA, [2]Department of Ophthalmology, Mayo Clinic, Rochester, MN, USA

Correspondence to: Dr. Carol L Shields, Ocular Oncology Service, 840 Walnut Street, Suite 1440, Philadelphia, PA 19107, USA. E-mail: carolshields@gmail.com

Received: 01-Apr-2019 Revision: 27-Apr-2019
Accepted: 25-Jun-2019 Published: 22-Nov-2019

Cite this article as: Camp DA, Dalvin LA, Schwendeman R, Lim LS, Shields CL. Outcomes of neonatal retinoblastoma in pre-chemotherapy and chemotherapy eras. Indian J Ophthalmol 2019;67:1997-2004.

Data collected included patient demographics (age, sex, race, family history of retinoblastoma, genetic testing, presenting symptom, laterality, and date of diagnosis), clinical features (International Classification of Retinoblastoma (ICRB) group, number of tumors per eye, largest basal diameter, thickness, anterior chamber seeds, iris neovascularization, vitreous seeds, subretinal seeds, and subretinal fluid), treatment methods (EBRT, plaque radiotherapy, focal therapy (transpupillary thermotherapy or cryotherapy) only, IVC, IAC, IVitC, enucleation, or exenteration), and treatment outcomes (tumor control, globe salvage, reason for enucleation, gross visual acuity, metastasis, second cancer, and death). Tumor control was defined as complete tumor regression prior to enucleation; eyes requiring enucleation for reasons other than tumor control (neovascular glaucoma and phthisis) were included in the total number of eyes with tumor control. Gross visual acuity was categorized as 20/200 or better (≥20/200), which included easy fix and follow, or worse than 20/200, which included poor or no fix and follow.

Data were tabulated using Microsoft Excel Version16.22 (Redmond, WA). A comparison by era (pre-chemotherapy vs. chemotherapy) of patient demographics, clinical features, treatment methods, and outcomes was performed, with Chi-square and Fisher's exact tests for categorical variables and Student's *t*-test for continuous variables.

Results

There were 128 eyes of 68 patients diagnosed with retinoblastoma within the first 28 days of life. These were divided into patients diagnosed in the pre-chemotherapy era (1980–1994) (n = 26) and the chemotherapy era (1995–2018) (n = 42).

Patient demographics are listed in Table 1. Comparison by era revealed no difference in patient age, sex, race, family history of retinoblastoma, genetic testing result, presenting symptom, initial laterality, eventual laterality, or study eye.

Table 1: Outcomes of neonatal retinoblastoma in pre-chemotherapy and chemotherapy eras. Demographics

Patient demographics	Pre-Chemotherapy Era (1980-1994) *n*=26 (%)	Chemotherapy Era (1995-2018) *n*=42 (%)	*P*	*n*=68 patients (%)
Age at presentation (days) Mean (median, range)	12 (10, 2-26)	15 (15, 1-28)	0.15	14 (13, 1-28)
Sex				
Male	12 (46)	20 (48)	0.99	32 (47)
Female	14 (54)	22 (52)		36 (53)
Race			0.45	
Caucasian	22 (85)	38 (90)		60 (88)
African American	3 (12)	3 (7)		6 (9)
Asian	1 (4)	0 (0)		1 (1)
Hispanic	0 (0)	1 (2)		1 (1)
Family history of retinoblastoma			0.43	
Yes	16 (62)	30 (71)		46 (68)
No	10 (38)	12 (29)		22 (32)
Genetic testing			**0.01**	
Available	2 (8)	16 (38)		18 (26)
Not available	24 (92)	26 (62)		50 (74)
	n=2 (%)	*n*=16 (%)		*n*=18 (%)
Genetic testing result			0.99	
Somatic mutation	0 (0)	1 (6)		1 (6)
Germline mutation	2 (100)	15 (94)		17 (94)
	n=26 (%)	*n*=42 (%)		*n*=68 (%)
Presenting symptom			0.65	
Family history	16 (62)	28 (67)		44 (65)
Leukocoria	8 (31)	11 (26)		19 (28)
Strabismus	1 (4)	2 (5)		3 (4)
Proptosis	1 (4)	0 (0)		1 (1)
13q syndrome	0 (0)	1 (2)		1 (1)
Laterality (initial)				
Unilateral retinoblastoma	12 (46)	16 (38)	0.61	28 (41)
Bilateral retinoblastoma	14 (54)	26 (62)		40 (59)
Laterality (eventual)				
Unilateral retinoblastoma	4 (15)	4 (10)	0.70	8 (12)
Bilateral retinoblastoma	22 (85)	38 (90)		60 (88)
	n=48 (%)	*n*=80 (%)		*n*=128 eyes (%)
Study eye			0.99	
Right eye	24 (50)	39 (49)		63 (49)
Left eye	24 (50)	41 (51)		65 (51)

Bold values indicate significant *P*

Clinical features at diagnosis are listed in Table 2. Comparison by era revealed no difference in ICRB group classification, mean number of tumors per eye, largest tumor diameter, tumor thickness, anterior chamber seeds, iris neovascularization, vitreous seeds, subretinal seeds, subretinal fluid.

Treatment methods are listed in Table 3. Comparison by era (pre-chemotherapy [Fig. 1] vs. chemotherapy [Figs. 2 and 3]) revealed that patients in the chemotherapy era were less frequently managed with primary EBRT (50% vs. 1%, $P < 0.001$) or plaque radiotherapy (17% vs. 0%, $P < 0.001$), and more frequently managed with primary IVC (0% vs. 81%, $P < 0.001$). Patients in the chemotherapy era more frequently required additional focal treatment only (10% vs. 45%, $P < 0.001$).

Sixty-five eyes of 35 patients received primary IVC, and 4 eyes of 3 patients received secondary IVC. Mean age at initial IVC was 1 month. Mean number of IVC cycles was 6. Chemotherapy consisted of vincristine, etoposide, and carboplatin ($n = 30$), vincristine and carboplatin ($n = 4$), vincristine and etoposide ($n = 1$), etoposide and carboplatin ($n = 1$), carboplatin only ($n = 1$), and an unknown regimen at an

Table 2: Outcomes of neonatal retinoblastoma in pre-chemotherapy and chemotherapy eras. Clinical features

Clinical features	Pre-Chemotherapy Era (1980-1994) *n*=48 (%)	Chemotherapy Era (1995-2018) *n*=80 (%)	*P*	*n*=128 eyes (%)
ICRB classification				
Group A	12 (25)	20 (25)	0.57	32 (25)
Group B	25 (52)	46 (58)		71 (55)
Group C	3 (6)	4 (5)		7 (5)
Group D	2 (4)	6 (8)		8 (6)
Group E	6 (13)	4 (5)		10 (8)
Number of tumors per eye Mean (median, range)	2 (1, 1-6)	2 (1, 1-6)	0.54	2 (1, 1-6)
Largest diameter (mm) Mean (median, range)	6 (4, 0.2-20)	6 (4, 0.1-24)	0.99	6 (4, 0.1-24)
Thickness (mm) Mean (median, range)	3 (2, 0.2-12)	3 (3, 0.1-14)	0.50	3 (3, 0.1-14)
Anterior chamber seeds	0 (0)	0 (0)	NA	0 (0)
Iris neovascularization	3 (8)	1 (1)	0.30	4 (3)
	n=43	*n*=71		*n*=114*
Vitreous seeds	1 (2)	0 (0)	0.38	1 (1)
Subretinal seeds	4 (9)	6 (8)	0.99	10 (9)
Subretinal fluid	10 (23)	21 (30)	0.52	31 (27)

ICRB=International Classification of Retinoblastoma, mm=millimeters, NA=Not applicable. *Information not available for some patients treated prior to being seen at our center

Table 3: Outcomes of neonatal retinoblastoma in pre-chemotherapy and chemotherapy eras. Treatment methods

Treatment methods	Pre-Chemotherapy Era (1980-1994) *n*=48 (%)	Chemotherapy Era (1995-2018) *n*=80 (%)	*P*	*n*=128 eyes (%)
Primary Treatment				
EBRT	24 (50)	1 (1)	**<0.001**	25 (20)
Plaque radiotherapy	8 (17)	0 (0)	**<0.001**	8 (6)
Focal only	10 (21)	11 (14)	0.33	21 (16)
IVC	0 (0)	65 (81)	**<0.001**	65 (51)
IAC	0 (0)	0 (0)	NA	0 (0)
IVitC	0 (0)	0 (0)	NA	0 (0)
Enucleation	5 (10)	3 (4)	0.26	8 (6)
Exenteration	1 (2)	0 (0)	0.37	1 (1)
Additional Treatment				
EBRT	6 (13)	5 (4)	0.33	11 (9)
Plaque radiotherapy	8 (17)	14 (18)	0.62	22 (17)
Focal only	5 (10)	36 (45)	**<0.001**	41 (32)
IVC	2 (4)	4 (5)	0.99	6 (5)
IAC	0 (0)	4 (5)	0.30	4 (3)
IVitC	0 (0)	2 (3)	0.53	2 (2)
Enucleation	6 (13)	4 (5)	0.17	10 (8)
Exenteration	0 (0)	0 (0)	NA	0 (0)

EBRT=External beam radiotherapy, IVC=intravenous chemotherapy, IAC=intra-arterial chemotherapy, IVitC=intravitreal chemotherapy, NA=not applicable. Bold values indicate significant *P*

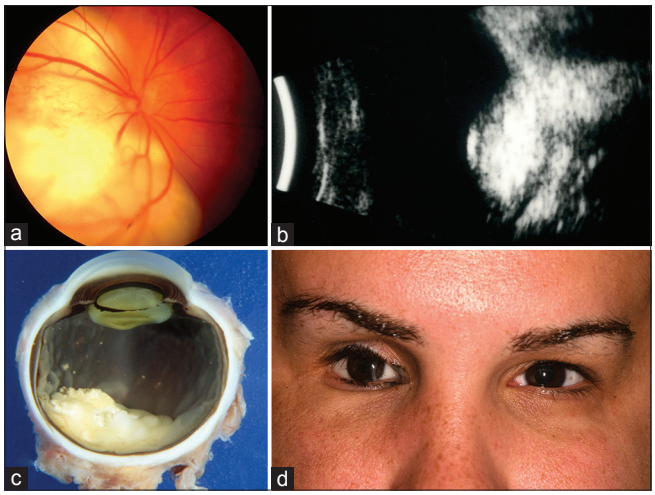

Figure 1: Neonatal retinoblastoma managed in the pre-chemotherapy era. (a) Large macular retinoblastoma in a 25-day-old female. (b) Ultrasonography showed echodense, calcified retinal mass with orbital shadowing. (c) Following external beam radiotherapy, recurrence necessitated enucleation. (d) At 27-year follow-up, there was orbital bone hypoplasia, more significant on the right side

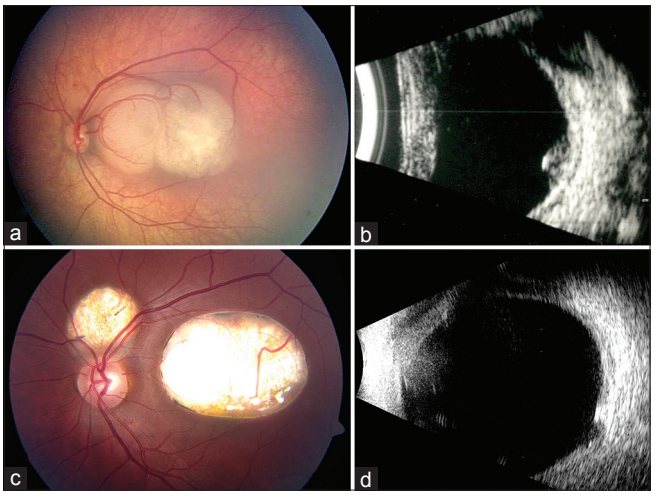

Figure 2: Neonatal retinoblastoma managed in the chemotherapy era. (a) Bilobed retinoblastoma in a 17-day-old male, (b) confirmed on ultrasonography, and following 6 cycles of intravenous chemotherapy and focal treatments (c) showed tumor regression (d) to flat remnants at 18-year follow-up. Visual acuity was count fingers at 1 foot

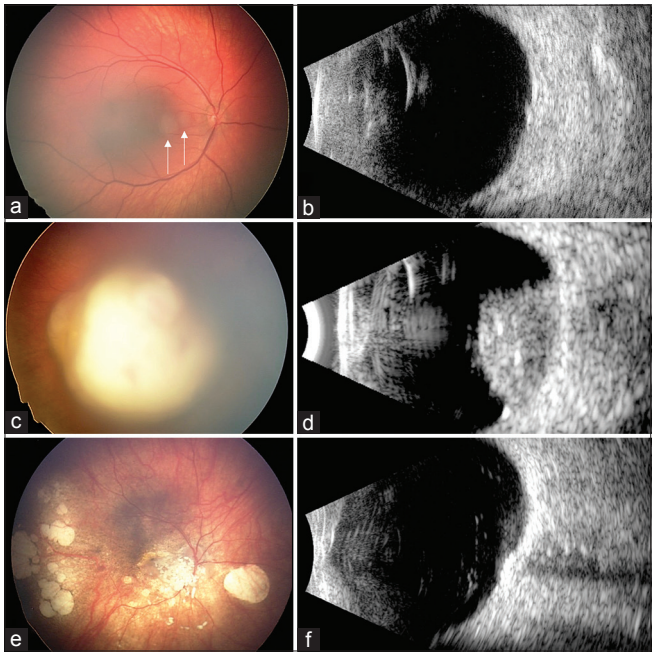

Figure 3: Neonatal retinoblastoma managed in the chemotherapy era with secondary intra-arterial chemotherapy. (a) Two small macular retinoblastomas (arrows) in a 6-day-old male, (b) confirmed on ultrasonography. (c) After primary treatment with intravenous chemotherapy, there was large recurrence, (d) confirmed on ultrasonography. (e) Following 4 sessions of intra-arterial chemotherapy, there was complete tumor regression (f) to flat remnants at 6-year follow-up. Visual acuity was 20/150

outside hospital (n = 1). Standard dosing was determined by body surface area. No ophthalmic or long-term toxicities were observed.

Four eyes of 4 patients received secondary IAC. Mean age at initial IAC was 6 months, and mean interval from start of primary IVC to initial IAC was 5 months. Mean number of IAC sessions was 4. Chemotherapy consisted of melphalan and topotecan (n = 4) and melphalan only (n = 2) with dose range of 3–7.5 milligrams (mg) melphalan and 1 mg topotecan. Complications included choroidal thinning (n = 1) and mottling of the retinal pigment epithelium (n = 1). For 1 patient, the neurosurgeon was unable to gain access during second IAC session, and no further attempts were made.

Two eyes of 2 patients received IVitC. A 12-year-old patient, initially treated with IVC and EBRT elsewhere, received 2 sessions of intravitreal melphalan at dose of 8 micrograms (μg) (recommended dose at that time in 2007) per session, and was subsequently treated with plaque radiotherapy and enucleation. A 2-year-old patient, initially treated with IVC at our institution, received 4 sessions of intravitreal melphalan dosed to 20 μg per session. Two months after first injection, mottling of the retinal pigment epithelium was noted.

Outcomes are listed in Table 4. A comparison by era (pre-chemotherapy vs. chemotherapy) revealed that patients in the chemotherapy era had significantly improved tumor control (79% vs. 94%, P = 0.02), globe salvage (75% vs. 91%, P = 0.02), final visual acuity (≥20/200: 66% vs. 89%, P < 0.01), and fewer deaths (19% vs. 0%, P < 0.01). Sub-analysis of eyes classified as group A compared by era revealed improved globe salvage (75% vs. 100%, P = 0.04).

Comparison by era revealed no difference in reasons for enucleation including primary treatment, solid tumor recurrence, neovascular glaucoma, and phthisis bulbi. There was no difference in metastasis or second cancer. Second cancers included pineoblastoma, rhabdomyosarcoma, and osteosarcoma. Causes of death included metastasis, second cancer, and respiratory failure.

In a sub-analysis of the chemotherapy era, a comparison of pre-IAC (1995–2008) (n = 58) and IAC (2009–2018) (n = 22) eras revealed that patients treated in the IAC era (4 received

Table 4: Outcomes of neonatal retinoblastoma in pre-chemotherapy and chemotherapy eras. Outcomes

Outcomes	Pre-Chemotherapy Era (1980-1994) *n*=48 (%)	Chemotherapy Era (1995-2018) *n*=80 (%)	*P*	*n*=128 eyes (%)
Follow-up (months) Mean (median, range)	125 (74, 4-330)	83 (75, 2-305)	0.07	99 (75, 2-330)
Tumor control per ICRB group	38 (79)	75 (94)	**0.02**	113 (88)
Group A	10 of 12 (83)	20 of 20 (100)	0.13	30 of 32 (94)
Group B	23 of 25 (92)	46 of 46 (100)	0.12	69 of 71 (97)
Group C	2 of 3 (67)	3 of 4 (75)	0.99	5 of 7 (71)
Group D	1 of 2 (50)	5 of 6 (83)	0.99	6 of 8 (75)
Group E	2 of 6 (33)	1 of 4 (25)	0.99	3 of 10 (30)
Globe salvage per ICRB group	36 (75)	73 (91)	**0.02**	109 (85)
Group A	9 of 12 (75)	20 of 20 (100)	**0.04**	29 of 32 (91)
Group B	23 of 25 (92)	45 of 46 (98)	0.54	68 of 71 (96)
Group C	2 of 3 (67)	3 of 4 (75)	0.99	5 of 7 (71)
Group D	1 of 2 (50)	5 of 6 (83)	0.99	6 of 8 (75)
Group E	1 of 6 (17)	0 of 4 (0)	0.99	1 of 10 (10)
Reason for enucleation	*n*=12*	*n*=7		*n*=19 eyes*
Primary treatment	6† (50)	3 (43)	0.99	9† (47)
Solid tumor recurrence	2 (17)	2 (29)	0.60	4 (21)
Neovascular glaucoma	1 (8)	2 (29)	0.52	3 (16)
Phthisis	1 (8)	0 (0)	0.99	1 (5)
Gross visual acuity of salvaged eyes	*n*=32‡	*n*=70‡		*n*=102 eyes‡
≥20/200	21 (66)	62 (89)	**<0.01**	83 (81)
<20/200	11 (34)	8 (11)		19 (19)
	n=26	*n*=42		*n*=68 patients (%)
Metastasis	1 (4)	0 (0)	0.38	1 (1)
Second cancer	3 (12)	1 (2)	0.29	4 (6)
Pineoblastoma	1 (4)	1 (2)	0.99	2 (3)
Rhabdomyosarcoma	1 (4)	0 (0)	0.38	1 (1)
Osteosarcoma	1 (4)	0 (0)	0.38	1 (1)
Death	5 (19)	0 (0)	**<0.01**	5 (7)
Metastasis	1 (4)	0 (0)	0.38	1 (1)
Second cancer	3 (12)	0 (0)	0.05	3 (4)
Respiratory failure	1 (4)	0 (0)	0.38	1 (1)

ICRB=International Classification of Retinoblastoma, ≥20/200=20/200 or better, <20/200=worse than 20/200. Bold values indicate significant *P*. *Two eyes were enucleated prior to being seen at our center and data were not available. †Includes one exenteration for extraocular extension of tumor. ‡Gross visual acuity at follow-up available for 32 eyes in the pre-IVC era and 49 eyes in the intravenous chemotherapy era

secondary IAC) had improved tumor control (91% vs. 100%, $P = 0.32$), globe salvage (89% vs. 95%, $P = 0.67$), and final visual acuity (≥20/200: 88% vs. 90%, $P = 0.99$), although these were not statistically significant.

Discussion

Retinoblastoma management has advanced dramatically in recent decades, resulting in improved clinical outcomes.[1-25] In a report by Selzer *et al*. on outcomes of retinoblastoma therapy in older patients (>5 years) per chemotherapy era, globe salvage was achieved in 8% in the pre-IVC era vs. 62% in the IAC era ($P < 0.001$), and compared to IVC (vs. IAC) avoidance of enucleation and external beam radiotherapy has improved (17% vs. 70%, $P = 0.03$).[36] However, there is no study to analyze these advancements regarding the neonatal population. Neonatal retinoblastoma patients often display familial retinoblastoma, bilateral disease, multiple tumors, macular involvement, and serious risks for trilateral retinoblastoma and second malignant neoplasms due to the high frequency of germline mutation.[5,26-35] In this study, we specifically focused on neonatal retinoblastoma in 68 consecutive patients based on era of treatment including pre-chemotherapy (1980–1994) and chemotherapy (1995–2018) eras. We found that tumor control, globe salvage, gross visual acuity, and survival for neonatal retinoblastoma patients significantly improved from the pre-chemotherapy to the current chemotherapy era, which encompasses the IAC era.

Previous studies have demonstrated that advancements in chemotherapy for retinoblastoma have improved globe salvage rates.[1-6,8-22] Globe salvage in the chemotherapy era using vincristine, etoposide, and carboplatin was achieved in over 90% of eyes classified as groups A, B, and C, 47% of group D, and 25% of group E eyes.[6] Using IAC, salvage of group D eyes improved to 94% and group E to 36%, with further improvement in these advanced cases using additional IVitC.[12,18]

Vitreous seeding often poses a risk to globe salvage, but IVitC can be remarkably effective in seed control and globe salvage. Shields *et al*. reviewed 40 consecutive eyes with viable vitreous tumor seeding treated with IVitC and documented complete seed resolution in 100% of eyes, and globe salvage in 88% of eyes.[19] By comparison per era (IAC without availability of IVitC (2008–2012) vs. IAC with availability of IVitC (2012–2015)) for retinoblastoma management of patients of all ages, Shields *et al*. noted that enucleation rates decreased (44% vs. 15%, P = 0.012) and particularly among group E eyes (75% vs. 27%, P = 0.039).[18] In a later report on 452 eyes treated with IAC for retinoblastoma by Francis *et al*., the authors found short one-year recurrence-free survival at 74% in the pre-IVitC era (May 2006–February 2013) and 78% in the IVitC era (February 2013–February 2017).[15] However, longer follow-up is needed to truly understand recurrence-free survival as most recurrences occur up to 3 years from treatment. An international collaborative effort from several institutions on 3553 injections of IVitC found this technique safe with no events of extrascleral extension.[37]

Few studies have reported data on clinical outcomes of neonatal retinoblastoma.[26-28] In 2002, Abramson *et al*. reported on 46 cases of neonatal retinoblastoma treated with EBRT (46%) vs. no EBRT (54%), noting that 33 of the total patients (72%) had family history of retinoblastoma.[27] Of 26 patients presenting with unilateral retinoblastoma, 22 (85%) developed bilateral involvement.[27] Globe salvage, based on Reese-Ellsworth Classification, revealed group I (39/40, 98%), group II (9/11, 82%), group III (8/8, 100%), group IV 4/5, 80%), and group V (1/11, 9%) eyes.[27] After mean follow-up of 10.9 years, death was documented in 8 (17%) cases from metastasis (4, 9%) or second cancer (4, 9%).[27] In 2006, Imhof *et al*. studied 12 cases of neonatal heritable retinoblastoma, of which 4 of 5 (80%) with unilateral retinoblastoma eventually developed bilateral involvement.[28] Globe salvage was achieved in 22 of 23 (96%) eyes.[28] In a report on 11 cases of neonatal retinoblastoma in 2017 by Kivelä *et al*., 7 (64%) had family history of retinoblastoma.[26] Of 8 patients presenting with unilateral retinoblastoma, 7 (88%) developed bilateral involvement.[26] Globe salvage was achieved in 18 of 21 (86%) eyes, metastasis occurred in no patients, and death occurred in 1 (9%) from a traffic accident.[26]

Previous studies have reported visual outcomes in eyes with retinoblastoma treated with chemotherapy.[7,38] In a report from our department on 140 eyes with retinoblastoma treated with IVC, visual acuity of 20/200 or better was achieved in 100 (71%) eyes, typically those with extramacular tumor and fewer number of tumors.[7] Fabian *et al*. reviewed 32 eyes with group D retinoblastoma treated with IVC and found risk factors (univariate analysis) for poor visual acuity to include younger age at presentation (P = 0.017), tumor location involving fovea at presentation (logarithm of the minimum angle of resolution (LogMAR) 1.42 ± 0.15 vs. 0.47 ± 0.22 (Snellen equivalent 10/263 vs. 20/59), P = 0.002), use of transpupillary thermotherapy (LogMAR 1.44 ± 0.20 vs. 0.79 ± 0.18 (Snellen equivalent 10/276 vs. 20/123), P = 0.026), and smaller tumor-foveola distance at last visit (P = 0.003).[38] However, on multivariate analysis, only transpupillary thermotherapy was significant (P = 0.010).[38]

In this current study, we found similar presenting features and outcomes compared to prior neonatal studies, in a relatively large cohort of 68 patients. In total, 46 of 68 (68%) patients had family history of retinoblastoma. Of 28 patients presenting with unilateral retinoblastoma, 20 (72%) developed bilateral involvement. Fifteen (79%) of 19 unilateral cases with family history developed bilateral involvement, and 5 (56%) of 9 with no known family history developed bilateral involvement. Tumor control was achieved in 38 of 48 (79%) eyes in the pre-chemotherapy era and 75 of 80 (94%) eyes in the chemotherapy era (P = 0.02). Globe salvage was achieved in 36 of 48 (75%) in the pre-chemotherapy era and 73 of 80 (91%) in the chemotherapy era (P = 0.02). Gross visual acuity was ≥20/200 in 21 of 32 (66%) salvaged eyes in the pre-chemotherapy era and 62 of 70 (89%) in the chemotherapy era (P < 0.01). There was a single case of metastasis in the pre-chemotherapy era and no metastasis in the chemotherapy era. Second cancer developed in 3 (12%) patients from the pre-chemotherapy era and 1 (2%) patient from the chemotherapy era. All 4 patients who developed second cancers had received EBRT in the pre-chemotherapy era (n = 3) or chemotherapy era (n = 1). The patient who developed second cancer in the chemotherapy era received only 1 cycle of chemotherapy due to detection of hearing loss. There were 5 (19%) deaths in the pre-chemotherapy era from metastasis (n = 1, 4%), second cancers (n = 3, 12%) (1 pineoblastoma, 1 rhabdomyosarcoma, 1 osteosarcoma), and respiratory failure (n = 1, 4%), and no deaths in the chemotherapy era (P < 0.01).

Previous studies have reported on costs associated with various treatment modalities for retinoblastoma, including IAC.[39,40] A study published in 2012 reported that the lowest-cost treatment strategy was enucleation ($48,000), followed by focal laser therapy ($100,250), systemic chemotherapy ($253,000), systemic chemotherapy with planned enucleation ($281,000), and lastly, intra-arterial melphalan chemotherapy (up to $430,000 for bilateral treatment).[39] In this report, compared to other age groups, patients diagnosed before age 6 months were most likely to have bilateral disease, most likely to receive chemotherapy, and least likely to undergo primary enucleation, suggesting that this age group faces the highest economic burden of treatment.[39] Three sessions of unilateral intra-arterial melphalan and 4 exams under anesthesia were calculated to cost $160,000, with each session of IAC costing $40,000.[39] However, in 2014, Ossandón *et al*. reported performing cost-effective IAC in Chile for only $3,651 per session.[40] The difference in cost suggests that a single regional analysis may not be generalizable and that actual IAC costs may depend heavily on specific healthcare systems.

Limitations of this study include its retrospective nature and small number of patients, given the rarity of the disease and the strict inclusion criteria for diagnosis within the first 28 days of life. Not all patients were initially seen at our center, which we acknowledge as an uncontrolled variable, but all were eventually managed at our center. Differences in presenting symptom, ICRB classification, and follow-up intervals between eras, although all not statistically significant, could have influenced the difference in rates of second cancer and death.

Conclusion

In summary, we have reported a cohort of neonatal retinoblastoma patients and, for the first time, compared outcomes for this age group by treatment era of pre-chemotherapy and

chemotherapy. Advancements in treatment of retinoblastoma, particularly the introduction of systemic chemotherapy and IAC, have improved tumor control, globe salvage, visual acuity, and survival from the pre-chemotherapy era to the current chemotherapy era for patients diagnosed within the first 28 days of life.

Financial support and sponsorship

Support provided in part by the ReMission Foundation (<remissionfoundation.org>) (CLS) and the Eye Tumor Research Foundation, Philadelphia, PA (CLS). The funders had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, or approval of the manuscript. Carol L. Shields, M.D. has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

There are no conflicts of interest.

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