Ocular Salvage and Vision Preservation Using a Topotecan-Based Regimen for Advanced Intraocular Retinoblastoma

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Published at ascopubs.org/journal/jco on October 10, 2016.

Support information appears at the end of this article.

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Presented in part at the 16th Biennial Meeting of the International Society of Ocular Oncology (ISOO), Cleveland, OH, September 29-October 3, 2013; 46th Congress of the International Society of Pediatric Oncology, Toronto, Ontario, Canada, October 22-25, 2014; and 17th ISOO Biennial Meeting, Paris, France, June 16-19, 2015.

Clinical trial information: NCT00186888.

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0732-183X/17/3501w-72w/\$20.00

ABSTRACT

Purpose

To evaluate topotecan-based therapy for advanced intraocular retinoblastoma.

Patients and Methods

Twenty-seven patients with bilateral retinoblastoma (male patients, $n = 14$; median age, 8.4 months) received chemotherapy: two courses of topotecan plus vincristine followed by three alternating administrations of carboplatin and vincristine for two courses and topotecan plus vincristine for one course, with optional periocular carboplatin. Focal therapy was applied after cycle 2. Event-free survival was defined as avoidance of external-beam radiotherapy (EBRT) and enucleation.

Results

Of 54 eyes, 42 were Reese-Ellsworth group IV to V, and 37 were International Classification of Retinoblastoma group C to E. Eleven eyes were enucleated: one at diagnosis, nine with progressive disease including three eyes treated with EBRT, and one that developed neovascular glaucoma after completion of therapy. One patient was removed from protocol with prolonged infection in course 1; 26 patients (51 eyes) were analyzed. At 10 years, cumulative incidence of EBRT was 5.9% ($SE \pm 3$), and event-free survival was 69.2% ($SE \pm 27.2$). Ocular survival for Reese-Ellsworth group IV to V eyes was 77.5% ($SE \pm 21.2$); it was 74.3% ($SE \pm 18.8$) for International Classification group C to E eyes. Vision testing (median age, 7 years; range, 5 to 10 years) documented 20/70 vision or better in one eye of 23 patients; 19 (76%) of 25 patients demonstrated 20/40 vision or better in one eye. All patients experienced thrombocytopenia (41 episodes in 275 courses; 15%). There were 29 episodes of febrile neutropenia (10%). Grade 3 diarrhea was present in nine of 27 patients, and one patient had an allergic reaction to carboplatin. All patients are alive at median follow-up 7.4 years (range, 2.7 to 10 years).

Conclusion

Topotecan combined with vincristine, carboplatin, and aggressive focal therapies is an effective regimen for the treatment of advanced retinoblastoma and results in globe salvage with vision. Toxicities were anticipated and managed with appropriate supportive care.

J Clin Oncol 35:72-77. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Retinoblastoma is the most common intraocular tumor of childhood and represents approximately 3% of all pediatric cancers.¹ Most patients in the United States present with localized intraocular disease, with excellent survival. Over the past two decades, the focus of therapy has shifted toward ocular salvage and vision preservation.

The goals of chemoreduction are to reduce tumor burden and facilitate local control with focal therapy. The selection and duration of systemic chemotherapy are based on the intraocular disease burden, laterality, and potential

for preservation of vision. The most commonly administered systemic chemotherapy combination is vincristine, carboplatin, and etoposide (VCE).²⁻⁵ Efforts to minimize the risk of etoposide-related secondary leukemia⁶ led to the preclinical discovery that the combination of topotecan and carboplatin was more effective (additive) in retinoblastoma cell lines and xenografts than either drug alone.^{7,8} Furthermore, periocular administration of carboplatin results in high intraocular concentrations with little systemic exposure.^{8,9} The goal of this study was to assess the efficacy of systemic topotecan when combined with vincristine and carboplatin in patients with advanced intraocular disease.¹⁰ Patients with residual or

ASSOCIATED CONTENT

Appendix

DOI: 10.1200/JCO.2016.69.2996

DOI: 10.1200/JCO.2016.69.2996

refractory vitreous seeding were eligible to receive periocular carboplatin for further disease control. Here we describe longer-term follow-up, including ocular salvage and vision, after topotecan-based therapy.

PATIENTS AND METHODS

Patient Population

RET5, a protocol for the study and treatment of patients with intraocular retinoblastoma, was approved by the St Jude Children's Research Hospital Institutional Review Board and open to accrual from February 4, 2005, through November 23, 2010. Written informed consent was obtained from each participant's parent or guardian. Eyes were grouped and enrollment was based on the Reese-Ellsworth (R-E) criteria,¹¹ because the study was designed when the International Classification (IC) of Retinoblastoma^{12,13} was still being evaluated. Patients were stratified into three groups: stratum A (early disease; R-E group I to III), stratum B (bilateral patients with worse eye R-E group IV or V), and stratum C (advanced unilateral retinoblastoma requiring immediate enucleation with risk-based adjuvant therapy dictated by pathologic findings). At the time of diagnosis, eyes were grouped using both R-E and IC criteria. For analysis, IC group C eyes were combined with IC groups D and E because of the increased risk of treatment failure in the presence of vitreous and/or subretinal seeding. Additional eligibility criteria included life expectancy longer than 8 weeks, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and adequate liver and renal function (total bilirubin, AST, ALT, and serum creatinine $< 3 \times$ normal). Patients with metastatic disease and active infection were excluded. This report focuses on patients treated in stratum B; results from strata C¹⁴ and A will be reported separately.

Treatment Plan

Chemotherapy was administered every 21 days (Appendix Table A1, online only). Patients in stratum B received neoadjuvant chemotherapy with two courses of vincristine and topotecan (VT; so-called window therapy), followed by vincristine and carboplatin (VC) in courses 3, 4, 6, 7, 9, and 10. VT was administered in courses 5, 8, and 11. As previously described,¹⁰ pharmacokinetically guided topotecan dosing was provided to attain a targeted systemic exposure of 120 to 160 ng/mL per hour. Carboplatin dosing was individualized after determination of the glomerular filtration rate, with an area under the curve of 6.5 mg/mL per minute. One dose of periocular (subtenon) carboplatin (20 mg/2 mL) was provided in courses 5, 8, and/or 11 (topotecan-containing cycles) to eyes with persistent vitreous disease at the discretion of the treating team. Focal treatments, including cryotherapy, laser photocoagulation, thermotherapy, and plaque radiotherapy, could be administered after the second course of chemotherapy.

Definition of Response

Documentation of retinoblastoma lesions during the examination under anesthesia using RET-CAM (Clarity Medical, Pleasanton, CA) was the primary evaluation of response to therapy. In addition, patients underwent magnetic resonance imaging (MRI) of both orbits and ultrasound evaluation of the involved eyes at baseline, after two courses, and at completion of all protocol therapy. Images were collected for future analysis of tumor response to systemic chemotherapy. Response to window therapy was previously reported.¹⁰ An event was defined as enucleation or external-beam radiotherapy (EBRT). Ocular survival and event-free survival (EFS) were documented per patient and per eye as follows. Ocular survival was defined per patient or per eye as the time interval from date of study entry to date of enucleation or date of last follow-up. EFS was defined per patient or per eye as the time interval from date of study entry to date of first event for an eye or to last follow-up date for patients or eyes without

events. For patients with bilateral advanced disease, time to the first event was used for the per-patient analysis.

Dose Modifications and Adverse Events

Adverse events (grade 3 to 5 or any unexpected grade 2) were monitored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Hematologic parameters before each course included absolute neutrophil count greater than 750/mm³ and platelets greater than 100,000/mm³ without transfusion. If chemotherapy was delayed more than 7 days in two consecutive courses because of neutropenia or thrombocytopenia, the doses of all cytotoxic agents were reduced by 20% in subsequent courses. The protocol was amended after the first 10 patients to implement granulocyte colony-stimulating factor administration starting 24 to 36 hours after completion of each course of topotecan until the absolute neutrophil count was greater than 2,000/mm³ after the nadir. Any grade 3 or 4 ocular or skin toxicity after periocular carboplatin precluded additional injections. Transient periorbital swelling (lasting 6 to 8 days) was expected and was not a limiting toxicity. Oral dexamethasone with ranitidine was provided after the procedure. Standard monitoring for nonhematologic toxicities was included.

Protocol Evaluations

Examinations under anesthesia were performed every 3 to 6 weeks during therapy, at the discretion of the treating team. MRI and ultrasound were performed as described. Patients receiving systemic carboplatin underwent audiology testing pretherapy (baseline) and after every third course of carboplatin. Glomerular filtration rate was determined by technetium-99m diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) scanning at baseline and after the third dose of carboplatin. Visual acuity testing was performed at each follow-up visit using age-appropriate measures. MRI of the brain and orbits was obtained at diagnosis, every 6 months for 24 months, and then every year for 3 years. Genetic counseling and testing for germline *RB1* mutation was provided for all patients. Research participants were referred to psychology and occupational therapy for additional neurocognitive and developmental research evaluations at baseline and at protocol-driven assessment time points.

Statistical Design and Analysis

The RET5 protocol was a single-arm, two-stage phase II study designed to evaluate response to window therapy as the primary objective. Accrual was slow in the first 2 years and then increased; however, with lower-than-expected accrual and evidence of efficacy (89%) in the first 27 patients treated with window therapy, the data safety monitoring board recommended closure of stratum B in June 2010. In the ocular survival analysis, an event was defined as enucleation, and in the EFS analysis, an event was defined as enucleation or EBRT. The Kaplan-Meier method was used to estimate ocular survival and EFS distributions. The log-rank test was used to compare survival distributions among patient groups. Gray's test was used to compare the cumulative incidence curves of EBRT between groups; enucleation before EBRT was considered a competing event in the cumulative incidence analysis.

RESULTS

Patients

A total of 103 patients were enrolled, of whom 101 were eligible for protocol treatment (Appendix Fig A1, online only). Twenty-seven patients (male, $n = 14$) with advanced bilateral retinoblastoma were enrolled in stratum B of RET5. Most patients were white, with a median age of 0.7 years at diagnosis (Table 1). One patient was removed from protocol because of toxicity

Table 1. Demographic Characteristics of RET5 Stratum B Patients

Characteristic	No. (%)
Sex	
Male	14 (51.9)
Female	13 (48.1)
Race	
White	21 (77.8)
Black	2 (7.41)
Other	2 (7.41)
American Indian or Alaskan Native	1 (3.7)
Asian	1 (3.7)
Enucleation	
Total No. of eyes	11 (20.4)
Total No. of patients	9 (33.3)
Age at primary diagnosis, years	
Median	0.7
Range	0.1-1.8
Time from primary diagnosis to last follow-up, years*	
Median	7.4
Range	2.7-10.0
Survival status at last follow-up*	
Alive	27 (100)

*Three patients who were not eligible for event-free or overall survival analysis are included.

(neutropenic colitis) after course 1, and one patient underwent enucleation of one eye at diagnosis; therefore, 51 eyes were included in the analysis. Of 51 eyes, 40 (78%) were R-E group IV to V, and 35 (69%) were IC group C to E (Table 2). Not all patients had advanced disease in both eyes, as summarized in Table 3, but all were candidates for conservative therapy to attempt bilateral ocular salvage. Two patients harbored a germline 13q deletion. Response to window (VT) therapy in this RET5 stratum B population has been reported elsewhere.¹⁰

Course and Dose Modifications

Twenty-four (89%) of 27 patients completed all courses of prescribed chemotherapy. One patient was removed from protocol after the first course because of prolonged neutropenia with viral gastroenteritis. Two patients developed progressive disease before course 3, requiring EBRT. Therapy, which was scheduled every 21 days, was delayed more than 7 days in five patients because of neutropenia (median, 12 days; range, 8 to 23 days), but none of the

Table 2. Classification of Eyes for RET5 Stratum B Patients

Classification Group	No.	%
Reese-Ellsworth		
I	1	1.85
II	4	7.40
III	7	12.96
IV	18	33.33
V	24	44.44
International Classification		
A	2	3.7
B	15	27.77
C	8	14.81
D	25	46.29
E	4	7.4

patients required dose reductions. Vincristine-related cranial neuropathy (swallowing difficulty) resulting in modification of vincristine therapy was noted in two patients.

Focal Therapy

Focal therapy was used to consolidate noncalcified portions of the tumor. Modality was selected at the discretion of the treating ocular oncologist. Green or diode laser was used for tumors located posterior or anterior to the equator of the globe. Tumors more proximal in location to the ora serrata were treated with cryotherapy. All eyes received focal therapy: cryotherapy (n = 107 episodes), green laser (n = 18 episodes), or diode laser (n = 408 episodes) after course 2 (Appendix Fig A2, online only). The second peak of focal therapy was noted at course 5, when local delivery of periocular carboplatin (C_{sc}) was allowed for patients with persistent vitreous or subretinal disease. When adjusted for total time at risk, there was no significant association between total number of focal therapies received per eye during chemoreduction and EFS ($P = .0989$) or ocular survival ($P = .1681$). C_{sc} was used in seven patients (eyes, n = 8): four patients received C_{sc} starting in course 5 (early group), and three patients received injections in courses 8 and 11 (late group). Periocular fibrosis was noted in all patients receiving periocular carboplatin, but it did not limit examination under anesthesia, nor did it necessitate later strabismus surgery. Seven patients (eyes, n = 8) were treated with iodine-125 plaque brachytherapy.

Outcomes

Because both patients who received EBRT eventually required enucleation of the eye(s), the 10-year EFS and ocular survival per patient were the same: 69.2% (95% CI, 0.158 to 1.0). The 10-year EFS and ocular survival per eye for all patients were also the same: 82.4% (95% CI, 0.484 to 1.0). Stratified by group, the 10-year EFS and ocular survival for R-E group I to III eyes were 100%; for R-E group IV to V eyes, they were 78% (SE $\pm$ 21%). By IC, the 10-year EFS and ocular survival per eye for group C to E eyes were 74% (SE $\pm$ 19%); of note, salvage was achieved in 100% of IC group C eyes. Salvage was achieved in all IC group A and B eyes. The cumulative incidence of EBRT for R-E group IV to V eyes (all IC group E) was 5.9% (SE $\pm$ 3%) at 10 years, with three eyes in two patients receiving EBRT for disease progression after course 4 (one patient, two eyes) or 5 (one patient, one eye) of therapy.

Ten eyes were enucleated: one at diagnosis, one because of neovascular glaucoma after therapy, one with hemorrhage related to tumor response during therapy, three (in two patients) that developed progressive disease during therapy (massive tumor recurrence, complete retinal detachment, and increased vitreous and subretinal seeding), and four that developed progressive disease after therapy (recurrence of main tumor and/or increased vitreous and subretinal seeding). In all cases of post-therapy enucleation, the contralateral eye had no active tumor. The three eyes enucleated after progressive disease development during therapy were treated with prior EBRT. Enucleated eyes were R-E groups IV (n = 2) and V (n = 8; IC groups D [n = 7] and E [n = 3]) at the time of diagnosis. No patient required additional treatment after enucleation (pT0, n = 1; pT1, n = 5; pT2, n = 4). No metastatic disease or secondary malignancy was reported, and all

Table 3. No. of RET5 Stratum B Patients in Each Disease Group (per eye)

	Right Eye		Left Eye		
	I	II	III	IV	V
Reese-Ellsworth group					
V	1	3	1	3	5
IV			2	2	5
III				3	1
II					1
I					
International Classification	A	B	C	D	E
E				1	1
D	2	5	1	3	1
C		2	1	3	
B		1		6	
A					

patients were alive at time of last follow-up (median, 7.4 years; range, 2.7 to 10 years).

Toxicity

Pancytopenia (grade 3 or 4) was the most common adverse effect. All patients experienced neutropenia, 25 patients experienced thrombocytopenia, and 23 patients experienced anemia. There were 215 episodes (in 270 courses) of grade 4 neutropenia (80%) and 41 episodes of grade 4 thrombocytopenia (15%); no grade 4 anemia was reported. Twenty-one patients received packed RBC transfusions, and 16 patients required platelet transfusions. There were two grade 4 nonhematologic toxicities: one patient with grade 4 diarrhea (after course 2 with topotecan) and one patient with an allergic reaction to carboplatin in the last course of therapy. Other grade 3 nonhematologic toxicities included diarrhea, mucositis, anorexia, dehydration, emesis, rash, and non-neutropenic fever (Table 4). Fever and neutropenia were reported in 16 patients (67%). When an etiology was identified, viral infections accounted for 40% (n = 15), whereas bacteremia was noted in three patients (13%; gram-positive organism, n = 2; nontuberculous *Mycobacterium*, n = 1). Vincristine-induced neurotoxicity was documented in

Table 4. Systemic Toxicity in RET5 Stratum B Patients

Adverse Event	No. of Patients	No. of Episodes	
		Grade 3	Grade 4
Febrile neutropenia	16	29	0
Absolute neutrophil count	27	63	215
Total WBC	21	28	7
Hemoglobin	23	70	0
Platelets	25	45	41
Diarrhea	9	11	1
Infectious diarrhea	1	1	0
Mucositis	2	2	0
Anorexia	8	11	0
Dehydration	5	5	0
Vomiting	2	3	0
Rash or desquamation	5	6	0
Allergic reaction or hypersensitivity (including drug fever)	2	1	1*
Fever (not neutropenic)	8	8	0
Infection	15	23	0

*Drug reaction to carboplatin.

two patients who recovered function after dose reduction and/or omission of vincristine. Ototoxicity (mild conductive hearing loss) was documented by routine screening in one patient (4%); no patient required hearing aids. Ocular toxicities associated with paired systemic topotecan and periocular carboplatin were limited to postinjection orbital inflammation and periocular fibrosis. There were no sight-threatening toxicities.

Visual Outcomes

Visual acuity was routinely observed. At a median age of 8 years (range, 5 to 11 years), all 24 patients (48 eyes) who completed therapy had documented vision: 29 eyes had measurable vision, six eyes could count fingers, three eyes could perceive hand motion, and two eyes had light perception only. Two eyes had no light perception, and six eyes were enucleated. Twenty patients (83%) had one eye with documented vision of 20/70 or better; 18 patients (75%) demonstrated at least 20/40 vision in one eye (Fig 1).

DISCUSSION

Topotecan was identified in preclinical testing,^{7,8} supported with phase I to II clinical data,^{15-20a} and translated into the RET5 protocol, a clinical trial for pediatric patients with advanced intraocular retinoblastoma. Importantly, preclinical pharmacokinetic data identified the effective duration of topotecan exposure^{19,20} to penetrate the blood-brain barrier²¹ and directly influenced the protocol schedule and dosing. Recommended age-appropriate dosages for topotecan in young children being treated at institutions that do not have resources for pharmacokinetic guidance for topotecan dosing have been previously published.¹⁰

Ocular salvage was achieved in 78% of eyes with advanced intraocular disease, when treatment included systemic vincristine, topotecan, and carboplatin combined with aggressive focal therapy. Measurable vision was preserved in more than 80% of patients. Furthermore, this approach limited the use of radiation therapy. Our results compare favorably with those of historical standards; EFS for R-E group IV to V eyes (IC groups C to E) treated with systemic chemotherapy and focal treatments has been considered to be 30% to 60%, although the reported follow-up has been limited (median, 13 or 20 months).^{5,22} Ocular salvage rates of 66% to 85% have been reported for group D retinoblastoma after intra-arterial chemotherapy, but studies have been limited by short follow-up, retrospective reporting, variable chemotherapeutic regimens, and a heterogeneous population.²³ One report of 5- to 10-year outcomes indicated 35% to 65% eye preservation for group C to E eyes treated with intra-arterial therapy.²⁴ One additional benefit of systemic therapy is the effect on micrometastatic disease, as suggested by the 20 published cases of systemic spread of disease after an exclusive intra-arterial approach.²⁵

Preservation of a globe is not synonymous with preservation of vision. Formal visual acuity metrics, such as the Snellen eye chart or Allen figures, are only useful in older survivors of retinoblastoma. Electroretinograms after therapy have been reported,²⁶⁻²⁸ but they are not a surrogate marker for vision; electroretinograms measure retinal function, not how the brain interprets the light signals from the retina. Although intra-arterial and intravitreal

Fig 1. Visual acuity after RET5 therapy. CF, count fingers; Enuc, enucleation; HM, hand motion; LP, light perception; NLP, no light perception. (*) $n = 1$. (**) $n = 2$. (***) $n = 3$.

routes²⁹⁻³³ of delivery have been advocated for use in patients with retinoblastoma, limited information regarding longer-term ocular salvage, late effects, and vision preservation in these patients is available. One report of vision preservation 5 to 15 years after intra-arterial chemotherapy documented visual acuity greater than 0.5 (better than 20/40) in 51% of eyes when the foveola was not affected by tumor.²⁴ Another report with 5-year follow-up after systemic chemoreduction with VCE reported visual acuity better than 20/40 in 50% of eyes, regardless of tumor location (90% if the tumor was extramacular in location).³⁴ In RET5, 10-year follow-up identified vision preservation of 20/40 or better in at least one eye in 75% of patients overall and 67% of patients with macular tumors (IC groups B to D) at diagnosis. Vision preservation after intravitreal chemotherapy has not yet been reported. Therefore, continued long-term follow-up is necessary to determine the functional outcomes and the role for each of the local delivery techniques in the overall treatment plan for patients with retinoblastoma.

The use of systemic topotecan produces pancytopenia, diarrhea, rash, and fever, which are managed with appropriate supportive care. However, systemic toxicity has been reported even with intra-arterial chemotherapy; neutropenia was documented in 30% of tested cycles (60% of total cycles).³⁵ There is no randomized study for toxicity comparison, but the prospective trial using VCE chemoreduction by Friedman et al⁵ provides a general overview. Patients in RET5 required more transfusions than patients receiving VCE. The number of central line infections (9%) in the Friedman et al study is similar to the three cases (13%) of bacteremia reported in our study, although no episodes of Gram-negative bacteremia were identified. GI toxicity (eg, diarrhea, anorexia, dehydration, and vomiting) was similar, whereas the incidence of vincristine-induced neurotoxicity was much lower

(8%) than that reported with the VCE regimen (40%). A prospective evaluation of topotecan-based chemoreduction in a multi-institutional study would provide further insight.

Preclinical evidence of an additive effect supports the administration of periocular carboplatin concurrently with systemic topotecan.^{7,8} The relative contribution of this approach to the results of our trial is unknown and is under investigation (SJRET6 trial; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01783535) identifier NCT01783535). Concerns regarding inflammation and ocular fibrosis have limited the widespread use of periocular carboplatin³⁶ and are being carefully monitored. Other methods for local delivery of carboplatin (eg, intravitreal) may provide the same efficacy with fewer ocular adverse effects ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02792036) identifier NCT02792036).

In summary, the incorporation of topotecan into first-line therapy for patients with advanced bilateral intraocular retinoblastoma and the improved rates of ocular salvage with useful vision clearly support the efforts to translate preclinical research into effective patient care. Intensification with topotecan and consolidation with aggressive local therapy provide a significant improvement in ocular survival with useful vision for survivors of advanced intraocular retinoblastoma. Topotecan in combination with carboplatin, vincristine, and aggressive focal therapy should be considered as first-line therapy for patients with advanced intraocular disease to achieve globe salvage with measurable vision.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

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Support

Supported in part by American Lebanese Syrian Associated Charities, Research to Prevent Blindness, St Giles Foundation, and National Institutes of Health Grants No. CA21765 and CA23099.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Ocular Salvage and Vision Preservation Using a Topotecan-Based Regimen for Advanced Intraocular Retinoblastoma

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/iffc.

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No relationship to disclose

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No relationship to disclose

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Acknowledgment

We thank Tracy Kaluzny, Vickie Given, Tammy Free, and Julie Overby-Canon for their assistance with patient care and data collection, and Alberto Pappo, MD, and Daniel Green, MD, for editorial assistance.

Appendix

Table A1. Doses for Chemotherapeutic Agents Used in RET5 Protocol, Stratum B	
Drug and Dose	Course
Vincristine	1-11
< 12 months: 0.05 mg/kg IV on day 1	
≥ 12 months: 1.5 mg/m ² IV on day 1 (maximum, 2 mg)	
Topotecan	1, 2, 5, 8, 11
Starting dose: 3 mg/m ² /day	
Target systemic exposure: 140 ± 20 ng/mL × hour	
Carboplatin	3, 4, 6, 7, 10
AUC 6.5 mg/mL/min IV on day 1	
Subconjunctival carboplatin*	5 and/or 8 and/or 11
20 mg/2mL × one dose	

Abbreviations: AUC, area under the curve; IV, intravenous.
*Optional.

Fig A1. RET5 patient enrollment and strata. R-E, Reese-Ellsworth.

Fig A2. Focal therapy delivered in RET5. OD, oculus dexter (right eye); OS, oculus sinister (left eye).