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Pathologic Risk-Based Adjuvant Chemotherapy for Unilateral Retinoblastoma Following Enucleation

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Abstract

Background—There are no standardized diagnostic or treatment guidelines for patients with advanced unilateral retinoblastoma.

Methods—Patients with advanced unilateral retinoblastoma were prospectively treated after enucleation using a risk-based protocol. Patients were assigned to low-risk (LR), intermediate-risk (IR), or high-risk (HR) based on pathology. LR patients underwent observation. IR patients received four courses of chemotherapy with vincristine, doxorubicin, and cyclophosphamide (VDC). In the HR group, patients received three courses of VDC alternating with three courses of vincristine, carboplatin, and etoposide (VCE) and irradiation when indicated.

Results—Fifty patients with advanced unilateral retinoblastoma were treated (LR n=36; IR n=7; HR n=7). All eyes were Reese-Ellsworth group V. All bone scans (n=81), lumbar punctures (n=16), and bone marrow aspirates (n=16) were negative. Chemotherapy was well tolerated. Grades 3/4 hematologic toxicities were seen in all patients; grades 3/4 non-hematologic toxicities were seen in half the patients. Only one patient in the HR group received radiation therapy. All

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patients were alive at the time of analysis with no signs of disease recurrence. Median follow-up was 3.4 years (range, 0.8-6.4 years).

Conclusions—Patients with non-metastatic unilateral retinoblastoma undergoing primary enucleation can be cured with a graduated-intensity approach based on pathology.

Keywords

retinoblastoma; unilateral; graduated; therapy; metastatic

INTRODUCTION

Retinoblastoma is the most frequent neoplasm of the eye in children and represents 3% of all pediatric cancers. Unilateral retinoblastoma constitutes approximately 70% of cases[1]. Most cases of unilateral retinoblastoma are advanced requiring enucleation. Following enucleation, treatment to minimize the risk of metastatic disease should be based on the pathologic evaluation of enucleated eyes[2]. However, there is no consensus on intensity and duration of chemotherapy[3-7]. Also, there is very limited data on the extent of metastatic workup required for patients with enucleated advanced unilateral retinoblastoma[8-11].

Herein we present our prospective protocol for an intensity graduated treatment based on pathologic risk features.

MATERIALS AND METHODS

Patients were enrolled on the institutional RET5 protocol if they met the following inclusion criteria: 1) newly diagnosed, previously untreated, intraocular retinoblastoma, 2) life expectancy greater than eight weeks, 3) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and 4) adequate liver and renal function as determined by bilirubin, SGOT, SGPT, and serum creatinine less than three times normal. Patients were excluded if they had presence of metastatic disease or if they had an active infection or were receiving antibiotics at the time of entry into the protocol. Patients were then stratified into three groups, Stratum A, B, or C. Stratum A included patients with early (Reese Ellsworth group I-III) bilateral or unilateral (unifocal or multifocal) retinoblastoma and patients with bilateral disease in whom the advanced eye had been enucleated upfront and the remaining eye had early stage disease. Stratum B included patients with bilateral retinoblastoma in whom at least one eye was Reese-Ellsworth group IV-V. Stratum C included patients with unilateral (unifocal or multifocal) retinoblastoma with advanced intraocular disease undergoing primary enucleation.

All Stratum C patients with unilateral retinoblastoma and advanced disease based on eye exam underwent upfront enucleation. All patients were offered genetic testing for RB1 mutation using mutation scanning through temperature modulated heteroduplix analysis which detects 75% of known mutations[12]. Patients in Stratum C were then divided into low risk, intermediate risk, or high risk groups based on the pathology of their tumors. Treatment was based on risk group. In the low risk group, pathology revealed no evidence of extraretinal disease. Pathology did confirm focal choroidal invasion without optic nerve

involvement, focal choroidal invasion with optic nerve involvement up to the lamina cribrosa, or optic nerve involvement alone up to the lamina cribrosa. No further treatment was given and patients were followed prospectively with clinical evaluation including exam, labs and MRI every six to twelve months. Since genetic testing at the time of the study was imperfect, our institutional standard was to perform EUAs as appropriate for age. In the intermediate risk group, pathology demonstrated presence of tumor cells in the anterior chamber, invasion of the ciliary body/iris, massive invasion of the choroid (>3mm), or invasion of the optic nerve beyond the lamina cribrosa with concomitant invasion of the choroid. These patients received chemotherapy consisting of four courses, every 21 days, of Vincristine, Doxorubicin, and Cyclophosphamide (VDC) followed by GCSF after each course of chemotherapy (Table I). In the high risk group, pathology showed sclera invasion and/or tumor at the cut end of the optic nerve. Patients in the high risk group were treated with six courses of chemotherapy consisting of three courses of Vincristine, Carboplatin, and Etoposide (VCE) alternating with three courses of Vincristine, Doxorubicin, and Cyclophosphamide (VDC), followed by GCSF after each course of chemotherapy (Table I). Baseline evaluations included an exam under anesthesia (EUA), magnetic resonance imaging (MRI), ultrasound, and RetCam imaging (Clarity Medical Systems). Following enucleation, additional testing and metastatic workup was performed for patients in the intermediate and high risk groups scheduled to receive chemotherapy. These tests included audiogram, glomerular filtration rate (GFR), echocardiogram, EKG, bone scan, lumbar puncture for cytology, and bilateral bone marrow aspirations and biopsies. The duration of each course of chemotherapy was 21 days and each course was only given if ANC >750/uL and platelets were >100,000/uL. If chemotherapy was delayed more than seven days due to neutropenia in two consecutive courses, the dose of all agents was decreased by 20%. If chemotherapy was delayed more than seven days in two consecutive courses due to thrombocytopenia, the dose of carboplatin was decreased to an area under the curve (AUC) of 5.5mg/ml/min in the high risk group. At the discretion of the treating team, patients in the high risk group could receive external beam radiation therapy (EBRT) to the entire orbit for a total dose of 45 Gy starting after two or three courses of chemotherapy.

RESULTS

One hundred and five patients were enrolled on the RET5 protocol from February 4, 2005 through November 11, 2010 and 57 of these were enrolled on stratum C. Two of these patients were considered to be ineligible and were excluded from analysis: one patient did not have a diagnosis of retinoblastoma after enucleation and the other patient was started on therapy with VCE for treatment of the contralateral eye prior to the final pathology report. There were five patients who had bilateral disease and received upfront enucleation of one eye; these patients were treated as a special group on stratum C based on the pathology of the enucleated eye and the Reese-Ellsworth grouping of the remaining eye. This report focuses on the 50 patients with unilateral disease who were treated on Stratum C of the RET5 protocol. Most patients (n=36; 72%) were treated on the low risk arm. Fourteen patients received chemotherapy on the intermediate or high risk arm (seven patients in each arm).

Table II shows characteristics for all unilateral stratum C patients by risk group. The median age at study enrollment for all patients was 26.4 months (range, 4.7 – 108.6 months). Gender was divided equally: 50% female and 50% male. The distribution of race was white (n=26; 52%), black (n=17; 34%), and other (n=7; 14%). Seven of 50 patients (14%) had RB1 germline mutations (one in the high risk, two in the intermediate risk, and four in the low risk groups). All eyes were Reese-Ellsworth group V (International Classification of Retinoblastoma: 22 group D and 28 group E). The median time from diagnosis by EUA to enucleation was two days (range, 0 to 13 days). For the 14 intermediate and high risk patients, the median time from enucleation to start of chemotherapy was 16 days (range, 7 to 23 days).

The pathologic characteristics of the enucleated eyes are listed in Table III. Histopathology risk features were defined by the degree of invasion of the choroid (minimal < 3mm, massive > 3mm), optic nerve (relative to the lamina cribosa), anterior chamber, iris, ciliary body, and sclera.

Bone Scans & Results

Eighty-one bone scans were done in 20 patients. All fourteen patients in the intermediate and high risk group were included and had a total of 70 bone scans. Six of the patients were in the low risk group and had a total of 11 bone scans. Bone scans were performed in these LR patients due to concerning clinical features found on EUA. The median number of bone scans per patient was 2.5 (range 1 – 11). The results for 80 bone scans were normal. For one patient, the result was inconclusive. To decrease the number of bone scans performed per patient and thus decrease the radiation exposure, the protocol was amended on August 25, 2009 to limit the performance of bone scans to at diagnosis only for IR and HR patients.

Metastatic Workup

Seventeen lumbar punctures and sixteen bilateral bone marrow aspirates and biopsies were performed in sixteen patients. One patient had two lumbar punctures due to a high white blood cell count in the first CSF sample. Two patients whose presenting clinical features were suspicious for high risk pathology, had a lumbar puncture and bone marrow aspirates and biopsies done during their enucleation to prevent extra sedation. These two patients were later classified as low risk after pathology was reviewed. All lumbar punctures and bone marrow procedures in IR and HR patients were performed prior to therapy at the time of central line placement under anesthesia; none showed evidence of metastatic retinoblastoma.

Treatment and Dose Modifications

The timing for follow-up EUAs for all patients was based on age, presence or absence of RB1 mutation and status of the remaining eye, with most EUAs occurring every three to six months. The seven intermediate risk patients each received four courses of chemotherapy with GCSF support for a total of 28 courses. Seven of the 28 courses were delayed: two in same patient due neutropenia, one due to an adenovirus infection, one due to surgical repair of orbital socket, and the remaining three for other non-treatment-related reasons (e.g., holiday or social reasons). All high risk patients received six courses of chemotherapy each

for a total of 42 courses. G-CSF was given with all courses except for one because the parent did not pick up the medication. In the high risk group, 6 of the 42 courses were delayed, two due to neutropenia, one due to fever, one due to viral illness, one due to orbital cellulitis, and one due to scheduling issues. In one patient, etoposide was omitted from one course due to an allergic reaction. Thus, for all intermediate and high risk patients, only 4 of 70 courses (6%) were delayed due to hematologic toxicity.

Only one patient received EBRT. This was a six year old boy who presented two weeks after sustaining trauma to his right eye. In the setting of a dense cataract and marked vitreous debris on ultrasound, an occult penetrating injury with endophthalmitis was suspected. Pars plana lensectomy and vitrectomy were performed. An intraocular mass was visualized and subsequent pathology review of the vitrectomy specimen showed small blue round cells. He was then referred for further evaluation. The diagnosis of diffuse infiltrating retinoblastoma was confirmed, and the eye was enucleated. Pathology of the eye showed involvement of the ciliary body and anterior chamber. Detailed examination of the vitrectomy sites showed no extraocular disease. He received 6 courses of VCE/VDC followed by EBRT (45 Gy) to the right orbit based on concern for tumor spread during the vitrectomy. Therefore, no patient in the high risk group received radiation based on pathology of the enucleated eye.

Toxicity

Table IV shows grade 3 and 4 toxicities (adverse events that were at least possibly related to treatment) by risk group. Grade 3 or 4 hematologic toxicities were seen in all 14 patients receiving chemotherapy: neutropenia (n=14), thrombocytopenia (n=6, HR), and anemia (n=4, IR; n=6, HR). Grade 3 or 4 non-hematologic toxicities were observed in seven patients (five high risk, two intermediate risk). These included dyspnea, febrile neutropenia, and diarrhea among other toxicities (Table IV).

Outcome

All patients were alive at the time of analysis and none had developed recurrence. The median follow-up from study enrollment to analysis was 3.4 years (range, 0.8 – 6.4 years).

DISCUSSION

Our study is a prospective, graduated intensity approach for adjuvant therapy based on pathologic findings of primarily enucleated eyes in patients with unilateral retinoblastoma. Chantada *et al* implemented a graduated intensity approach in a prospective study[4], but included patients with bilateral and unilateral disease, as well as eyes enucleated post chemotherapy. In our study, all 36 patients with low risk pathologic findings are alive without evidence of disease following observation. This is important since many patients in this group had focal choroidal invasion (n=13) and/or some degree of optic nerve involvement (n=27), as seen in Table III. In a retrospective study, Guillermo *et al* similarly observed that patients with no high risk pathology factors and those with pathology risk factors including isolated choroid invasion or post-laminar optic nerve involvement without choroidal or scleral involvement could be followed without adjuvant therapy[3].

The 14 patients in the intermediate risk and high risk groups were successfully treated with no evidence of recurrence after only four and six cycles of adjuvant chemotherapy, respectively. Our results are similar to a recently published study by Aerts et al where IR and HR patients received four and seven cycles of chemotherapy respectively[13]. Others have shown that patients with high risk histopathology features can be managed with conventional chemotherapy, but used more aggressive or protracted regimens (Table V). On the other hand it is possible, as suggested by Aerts et al, that many of our patients in the IR and HR groups did not require chemotherapy and received unnecessary toxicity from the invasive procedures and chemotherapeutic agents[13]. To better distinguish between true vs. theoretical risk patients a larger randomized study and better detection methods of retinoblastoma “tumor markers” such as the ganglioside GD2 synthase in the CSF and bone marrow are needed[14].

Since the toxicity data was collected prospectively in our study, it provides a good reference on expected toxicity in these age groups. The toxicity profile of our patients was acceptable with G-CSF support (Table IV). It is not possible to compare our prospective data with other retrospective studies in the literature.

Prior to the initiation of therapy, patients in the intermediate and high risk groups underwent a metastatic work up including bone scan, lumbar puncture, and bilateral bone marrow aspirates and biopsies. All evaluations were negative for evidence of metastatic disease. Clinical evaluation did not reveal laboratory evidence or symptomatic history concerning for metastatic disease. The negative findings in our study are important to note due to cost and potential morbidity associated with each procedure[15,16]. Since none of the bone scans performed in our cohort were positive and scans are associated with an increased dose of radiation in this sensitive population[17], we do not recommend bone scans as part of the routine metastatic workup for patients with no evidence of orbital extension or metastatic disease.

In conclusion, though our numbers are small, this prospective study provides justification of a graduated intensity approach to adjuvant therapy based on histopathology following primary enucleation in patients with non-metastatic, unilateral retinoblastoma. Patients with the highest risk histopathology features were adequately treated with less chemotherapy and did not require radiation therapy. Though the metastatic work-up in all our patients was negative, we caution that clinicians must weigh the cost of the procedures with the ultimate risk of under-treating a child with high risk disease. Clinical findings (i.e. bony pain, low peripheral blood counts indicating possible bone marrow suppression) are not sensitive or specific enough to confidently guide the selection of patients for metastatic work-up[18]. Continued correlation of work-up with clinical assessments will provide continued guidance for this at-risk group of patients.

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Table I

Chemotherapeutic Treatment in Stratum C

Intermediate Risk Group		
Drug	**Age <12 months**	**Age >12 months**
Vincristine	0.05 mg/kg IV day 1	1.5 mg/m^2 IV day 1 (max 2 mg)
Cyclophosphamide With Mesna 200 mg/m^2 at 0, 3, 6, and 9 hours.	40 mg/kg IV day 1	1,200 mg/m^2 IV day 1
Doxorubicin	1.5mg/kg IV day 1	45 mg/m^2 IV day 1
GCSF 5 mcg/kg/day until ANC >2000/uL after nadir.		
High Risk Group		
Drug	Age <12 months	Age >12 months
Courses 1,3, 5:		
Vincristine	0.05 mg/kg IV day 1	1.5 mg/m^2 IV day 1 (max 2 mg)
Carboplatin	*administered IV to achieve an AUC of 6.5 mg/ml/minute on day 1.	*administered IV to achieve an AUC of 6.5 mg/ml/minute on day 1.
Etoposide	3.3 mg/kg/day IV days 1-3	100 mg/m^2/day IV days 1-3
GCSF 5 mcg/kg/day until ANC >2000/uL after nadir.		
Courses 2, 4, 6		
Vincristine	0.05 mg/kg IV day 1	1.5 mg/m^2 IV day 1 (max 2 mg)
Cyclophosphamide With Mesna 200 mg/m^2 at 0,3,6, and 9 hours.	40 mg/kg IV day 1	1,200 mg/m^2 IV day 1
Doxorubicin	1.5mg/kg IV day 1	45 mg/m^2 IV day 1
GCSF 5 mcg/kg/day until ANC >2000/uL after nadir.		

Table II

Patient Characteristics for RET5 Stratum C Patients with Unilateral Disease (n=50)

	Risk Group			All Unilateral Stratum C Patients (n=50)
	High	Intermediate	Low	
	N=7	N=7	N=36	
Age at Study Enrollment (months)				
Median (Range)	24.4 (17.2-71.5)	13.1 (6.1-28.6)	29.4 (4.7-108.6)	26.4 (4.7-108.6)
Age at Diagnosis (categorical)				
Birth - <12 months	0	3	5	8 (16%)
≥12 months - <60 months	6	4	25	35 (70%)
≥60 months	1	0	6	7 (14%)
Gender				
Male	3	4	18	25 (50%)
Female	4	3	18	25 (50%)
Race				
White	4	5	17	26 (52%)
Black	2	2	13	17 (34%)
Other	1	0	6	7 (14%)
Reese-Ellsworth Group				
VA	1	3	4	8 (16%)
VB	6	4	32	42 (84%)
International Classification of Retinoblastoma				
Group D	0	3	19	22 (44%)
Group E	7	4	17	28 (56%)

Table III

Histologic characteristics of the enucleated eye by risk group

Group	Anterior Chamber	Iris	Ciliary Body	Choroid			Optic Nerve					Sclera
				None	Focal	Massive	None	Pre-laminar	Laminar	Post Laminar	Cut End	
LR (n=36)	0	0	0	23	13	0	9	18	6	3	0	0
IR (n=7)	0	1	1	0	0	7	0	2	2	3	0	1[a]
HR (n=7)	3	3	3	1	1	5	1	0	4	2	0	7

Abbreviations: LR, low risk; IR, intermediate risk; HR, high risk

[a] Initially, this patient was not found to have scleral involvement and was classified as IR. Later, pathology was revised on review of enucleated eyes but the patient remained in the IR group.

Table IV

List of Grade 3/4 Toxicities by Risk Group

Toxicity	Risk Group			
	Intermediate		High	
	Grade 3	Grade 4	Grade 3	Grade 4
	N	n	n	n
Hematologic Toxicities				
Anemia	4		5	1
Total White Blood Cell count	3	3	4	2
Neutropenia	2	5	2	5
Thrombocytopenia			4	2
Non-hematologic Toxicities				
Elevated transanimases			1	
Allergic reaction/hypersensitivity (including drug fever)			1	
Diarrhea	1			
Dyspnea				1
Febrile neutropenia	1		1	
Hypoxia			1	
Infection with normal ANC or Grade 1 or 2 neutrophils, Lung (pneumonia)			1	
Infection with normal ANC or Grade 1 or 2 neutrophils, Skin (cellulitis)			1	
Infection with normal ANC or Grade 1 or 2 neutrophils, Upper airway NOS	1			
Nausea			1	
Hypophosphatemia			1	
Hypokalemia			1	
Vomiting			1	

Table V

Summary of Studies Treating Retinoblastoma with High Risk Features after Enucleation

Source	Location	Study Type	High Risk Features Defined	Total Number of pts	# of eyes enucleated up front	Chemotherapy for enucleated eyes with High risk pathology	Radiation	Outcome
Kaliki, 2011[19]	Philadelphia, PA	Retrospective	Invasion into anterior segment, >=3mm post. uvea, PLONI, or post uvea + optic nerve involved.	51 (32 UL, 19 BL)	46/52	6 courses of Vincristine 0.05 mg/kg, Etopophos 5mg/kg, Carboplatin 18.6 mg/kg.	None	All patients alive without mets @ 66 mo
Luna-Fineman, 2011[20]	Central America	Prospective	Massive choroidal, scleral, or optic nerve beyond the lamina cribrosa involvement.	171 (129 UL, 42 BL)	6+	Enucleation only for tumor confined to retina. Enucleation followed by 6 courses of VCR 1.5mg/m2, Etoposide 100mg/m2 (× 3days), Carboplatin 500 mg/m2 [2-3 course of chemo first if buphthalmos was present] if + high risk features.	Radiation for eyes with local regional extension (40-50 Gy).	89 alive, 44 dead, 34 abandoned tx, 4 refused tx after enrollment.
Gao, 2011[21]	Shanghai, China	Retrospective	Not defined.	133 (107 UL, 26 BL)	123	6 courses of VCR 1.5mg/m2, Etoposide 150mg/m2 (× 2days), and Carboplatin 560mg/m2.	As salvage therapy.	Cumulative probability of survival -98% at 60 months
Chantada, 2010[5]	Buenos Aires, Argentina	Prospective	1)Post-laminar optic nerve involvement (PLONI) with full choroid or scleral invasion, 2) tumor at the optic nerve resection margin, 3)any scleral invasion, or 4) PLONI with tumor more than 1mm beyond the lamina cribrosa or >20% of whole optic nerve stump.	114 (all UL)	95	Group 3: High risk features. Enucleation followed by 8 cycles of chemotherapy – Carboplatin 500mg/m2 × 2days, Etoposide 100mg/m2 × 3days, Cyclophosphamide 65mg/kg/day, and Idarubicin 10mg/m2/day, and VCR 1.5mg/m2/day.	Group 3 – after enucleation if + tumor invasion to optic nerve cut end -45 Gy.	5 y EFS 94%
Atchaneeyasakul, 2009[22]	Bangkok, Thailand	Retrospective	Massive choroid invasion, extensive tumor necrosis, tumor angiogenesis, optic nerve head invasion.	90 (59 UL, 31 BL)	51 UL 31 BL	6 cycles of Carboplatin, Etoposide, and VCR.	Yes, for 7 patients.	11 alive with disease, 66 alive without disease, 7 dead

Source	Location	Study Type	High Risk Features Defined	Total Number of pts	# of eyes enucleated up front	Chemotherapy for enucleated eyes with High risk pathology	Radiation	Outcome
Chantada, 2004[4]	Buenos Aires, Argentina & New York City, NY	Retrospective	Involvement of the anterior chamber, choroid (isolated), PLONI, sclera.	224 (all UL)	All	No chemo for isolated choroid or anterior chamber. PLONI (+) margin – Before 1994 – 19 wks of VDC, 6 wks intrathecal chemo. After 1994 – 8 wks of chemo (VCR/Cyclophosphamide/ Idarubicin + Etoposide/ Carboplatin). PLONI (-) margin–Before 1994 -19 weeks of VDC & 6 weeks intrathecal chemo. After 1994 – 8 wks of chemo (Vcr/ Cyclophosphamide + Etoposide/Carboplatin).	PLONI with invasion at cut end -40-45Gy	3 y EFS 90% 3y OS 96%

Abbreviation: UL, unilateral; BL, bilateral; VCR, vincristine; PLNOI, post laminar optic nerve invasion; VDC, vincristine, doxorubicin, and cyclophosphamide