Published in final edited form as:

Pediatr Blood Cancer. 2016 November ; 63(11): 1954–1958. doi:10.1002/pbc.26138.

Patients with Retinoblastoma and chromosome 13q deletions have increased chemotherapy-related toxicities

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Abstract

Background—Five-10% of retinoblastoma (RB) patients harbor deletion of chromosome 13q (13q-). Treatment related toxicities in this population have not been described.

Methods—Sixty-eight RB patients on a single institutional protocol (RET5) from 2005–2010 were reviewed. Genetic screening identified eleven patients (7 female) with 13q-. Patients with early (Reese-Ellsworth [R-E] group I–III) disease (6/23 with 13q-) received 8 courses of vincristine/carboplatin (VC). Patients with advanced (R-E group IV–V) bilateral disease (2/27 with 13q-) received 2 courses of vincristine/topotecan (VT) followed by 9 courses of alternating VT/VC. Patients undergoing upfront enucleation received histopathology-based chemotherapy: intermediate risk (2/8 with 13q-) or high risk (1/10 with 13q-). Dose reductions were mandated for >7 day delay in 2 consecutive courses following hematologic toxicity. Grade 3 and 4 hematologic, infectious, and gastrointestinal toxicities were compared between RET5 patients with and without 13q-.

Results—Demographics were similar between groups. When present, prolonged neutropenia (median 7 days, range 0–14 days) delayed chemotherapy and resulted in more frequent dose reductions among 13q- patients (5/11) than non-13q- patients (4/57) ($p < 0.01$). GI toxicity was similar between groups (5/11 13q- vs. 13/57 non-13q-) ($p = 0.14$), but halted chemotherapy in one

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This work was previously presented, in part, at the International Society of Ocular Oncology (2011) and American Society of Pediatric Hematology Oncology (2012) meetings

Disclaimer: None of the authors have any conflicts of interest or financial disclosures

13q- patient. Infectious complications and disease outcomes were similar between groups. At follow-up, all patients are alive (median 6.1 years, range 7.6 months to 9.5 years).

Conclusion—13q- RB patients had a higher incidence of neutropenia requiring chemotherapy dose reductions, but did not have increased treatment failure.

Keywords

13q deletion syndrome; 13q-; retinoblastoma; chemotherapy-related toxicity; neutropenia

Introduction

Retinoblastoma is the most common intraocular malignancy of childhood, and is fatal if untreated. Biallelic inactivation of the tumor suppressor gene, *RB1*, has been identified in virtually all tumors and is a critical factor in retinoblastoma tumorigenesis.

While most patients with heritable retinoblastoma undergo a mutation of one *RB1* allele as the “first hit,” a small group of patients have a complete deletion of the long arm of chromosome 13 (13q- syndrome, “13q-”) which contains the *RB1* gene.^{1–4} The remaining copy of *RB1* is normal but silenced through other mechanisms, such as loss of heterozygosity or epigenetic dysregulation.^{5–7} Patients with 13q- have considerable phenotypic variability, exhibiting a spectrum of dysmorphic features and systemic complications, including gastrointestinal tract abnormalities and failure to thrive.^{8–10} While a deletion of 13q in the tumor cells of children with other malignancies, such as Burkitt lymphoma,¹¹ has been shown to negatively impact prognosis, it is not known if 13q- impacts therapy or prognosis for retinoblastoma patients. Previously, the outcome¹² and radiographic findings¹³ of five patients with 13q- treated at St. Jude Children’s Research Hospital (SJCRH) were reported. Therapy for retinoblastoma has since evolved with emphasis on chemoreduction and decreased use of external beam irradiation. Therefore, we retrospectively reviewed our retinoblastoma population to identify the clinical features and frequency of treatment related toxicity in patients with 13q- treated on a single protocol over a five year period.

Materials and Methods

After SJCRH Institutional Review Board (IRB) approval, we retrospectively reviewed an institutional Health Insurance Portability and Accountability Act (HIPAA)-compliant database for patients treated between February 2005 and September 2010 (n=105) on a single IRB approved protocol for patients with newly diagnosed intraocular retinoblastoma (“RET5;” NCT00186888). Demographic and clinical information, including phenotypic manifestations of 13q-, therapy and outcomes were reviewed. Specifically, grade 3 or grade 4 hematologic (hemoglobin, platelets, and absolute neutrophil count [ANC]), infectious (febrile neutropenia, bacteremia), and gastrointestinal (GI) toxicities (anorexia, dehydration, emesis) were reviewed based on the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTC-AE), including duration of each event and impact on subsequent therapy such as delay, reduction of chemotherapy dosage, or removal from therapy.

Testing for the presence or absence of germline *RBI* mutation was performed in all patients. Further testing with cytogenetics, including fluorescent in-situ hybridization (FISH) with an internal control probe for 13q, was performed as a second-line test if germline testing was negative in patients with bilateral disease, those who were less than one year of age at diagnosis regardless of laterality, or those who exhibited suspicious delay in growth, cognitive function or development. While older age does not exclude a germline abnormality in *RBI*,¹⁴ age < 1 year at diagnosis was used as a proxy for possible heritable patients and therefore additional testing. Sub-microscopic deletions were defined as those deletions of chromosome 13q only detectable by FISH; other deletions were defined as identifiable by conventional cytogenetics.

Patients enrolled on RET5 protocol therapy were stratified by laterality and Reese-Ellsworth (R-E) Group.¹⁵ Courses of therapy were administered every 21 days. The doses of chemotherapeutic agents are listed in Supplemental Table 1. Patients on Stratum A (unilateral or bilateral R-E I–III) received neoadjuvant vincristine and carboplatin (VC) for a total of eight courses. Stratum B patients (bilateral disease with worse eye R-E IV or V) received neoadjuvant chemotherapy: two courses of vincristine and topotecan (VT)¹⁶, followed by VC in courses 3, 4, 6, 7, 9, and 10. VT was given in courses 5, 8 and 11. Periocular (subtenon) carboplatin was optional for residual vitreous disease; no 13q- patient required this intervention. Patients who required initial enucleation (Stratum C; RE IV–V unilateral) were further stratified to low, intermediate and high risk groups based on histopathologic exam of enucleated eyes, as previously reported; only intermediate and high risk groups received adjuvant chemotherapy.¹⁷ All patients with bilateral disease who required upfront enucleation received adjuvant chemotherapy. External beam radiation therapy (EBRT) was considered for patients with extraorbital extension (EOE) in the high risk group, but did not apply in the 13q-population as no patients had EOE.

For all patients receiving neo-adjuvant chemotherapy, focal treatments including cryotherapy, laser photocoagulation, thermotherapy, and plaque radiotherapy could be administered after the second course of chemotherapy. Examinations under anesthesia were performed every three to six weeks during therapy, at the discretion of the treating team.

Hematologic parameters required prior to each course included absolute neutrophil count (ANC) >750/mm³ and platelets > 100,000/mm³ without transfusion. If chemotherapy was delayed more than 7 days in two consecutive courses due to thrombocytopenia or neutropenia, the dose of myelosuppressive chemotherapy agents was reduced by 20% in subsequent courses. Granulocyte colony stimulating factor (GCSF) starting 24–36 hours after completion of chemotherapy until ANC >2000/mm³ after the nadir was administered following all courses of topotecan. Any patient who developed an allergic reaction to etoposide subsequently received etoposide phosphate.

STATISTICAL ANALYSIS

There were two groups for comparison: the 13q- population (n=11) was compared to all other patients who received chemotherapy as part of the institutional RET5 protocol (n=57). Fisher's exact test was used to compare distributions of sex and race among patient groups and the exact Wilcoxon rank sum test was used to compare the distribution of age at

diagnosis among groups. The exact Kruskal-Wallis test was used to compare the distribution of stratum among patient groups. Proportions of patients experiencing delay, dose reduction and specific toxicities (e.g., grade 3/4 neutropenia, thrombocytopenia, anemia, etc.) were compared among patient groups using Fisher's exact test. The method of generalized estimating equations was used to examine the association between delay in chemotherapy cycles and 13q- status. The exact Wilcoxon rank sum test was used to compare numbers of toxic episodes per patient among patient groups. SAS (version 9.3) and StatXact PROCs (Cytel Studio) were used for statistical analyses. P-values <0.05 were considered statistically significant.

Results

A total of 105 patients with intraocular retinoblastoma were enrolled on RET5. Eleven patients (10%), 7 female, were identified with deletion of 13q. Four patients had sub-microscopic 13q deletions in all of the 200 nuclei evaluated and one additional patient had a sub-microscopic 13q deletion in 80% of the nuclei. Five patients had 13q deletions identified by conventional cytogenetics and 1 patient had a complex chromosomal rearrangement resulting in loss of *RB1* on chromosome 13. Patients with 13q- were not statistically different with respect to gender, age at diagnosis, or laterality from their non 13q- counterparts treated on the RET5 protocol (Table 1).

Sixty-eight RET5 patients, including all 11 with 13q-, received chemotherapy. Twenty-three patients were treated on stratum A (6/23 with 13q-). Twenty-seven patients were treated on stratum B (2/27 with 13q-). Eighteen patients were treated on stratum C for intermediate risk (IR) (2/8 with 13q-) or high risk (HR) (1/10 with 13q-) histopathology features; Stratum C included patients with bilateral disease who required upfront enucleation (0/5 with 13q-).

Grade 3 or 4 neutropenia was reported in all patients receiving chemotherapy (Table 2). Dose reductions due to neutropenia were more frequent in patients with 13q- (5/11; 45% (95% Blyth-Still-Casella confidence interval (CI), 20%–75%)) than in other patients (4/57; 7% (95% CI, 2%–17%), $p<0.01$). No significant differences in the incidence of grade 3 or 4 anemia or thrombocytopenia were seen between groups (Table 3).

GI toxicity (anorexia, dehydration or emesis) was noted in both groups and was not statistically different (Table 3). GI toxicity (specifically, grade 3 anorexia and emesis) led to cessation of protocol chemotherapy after one course of therapy in one 13q- patient whose weight was <3rd percentile for age at the time of diagnosis. This patient continued to have difficulty with feeding after therapy, requiring total parenteral nutrition, and was diagnosed with gastroparesis and oral aversion. A gastrostomy tube was required to provide complete nutritional support.

Bacteremia and febrile neutropenia was noted in both 13q- and non-13q- patients (Table 3). One non-13q- patient had grade 4 bacteremia. No patient had grade 4 febrile neutropenia in either group.

Overall, the total number of episodes per patient of grade 3 and 4 toxicity was not statistically different between the 13q- population (115 total episodes, median 10 per patient,

range 2 to 25) and the non-13q- patients (753 total episodes, median 12 per patient, range 2 to 27) ($p=0.30$). Grade 3 and 4 toxicities were compared between those 13q- patients with sub-microscopic deletions ($n=5$; median 12 episodes per patient, range 2–25) compared with 13q- patients who had 13q deletions identifiable by conventional cytogenetics ($n=5$, median 6 episodes per patient, range 4–14); this was not statistically significant ($p=0.55$).

Other significant AEs related to RET5 therapy were reviewed and are reported in Table 3. Numbers were too small for meaningful statistical analysis. There was no grade 3 or 4 vincristine-related peripheral neuropathy. Hyperthermia following anesthesia was reported in two 13q- patients, but in no patients without 13q-.

One patient with 13q- experienced progressive disease during therapy. This patient had a reduction of carboplatin dose due to prolonged neutropenia and thrombocytopenia. Five of the 57 patients without 13q- had progressive disease, two of whom had reduced vincristine dosages during therapy due to vincristine-induced neuropathy. Despite further focal therapy, all patients with progressive disease, regardless of 13q status, required enucleation; all patients are alive. One patient with 13q- and corpus callosum agenesis, who only completed 4 of 8 courses of chemotherapy due to prolonged neutropenia and toxicity with systemic chemotherapy, developed trilateral retinoblastoma four years after diagnosis of unilateral retinoblastoma. The enlargement of the pineal gland was noted on routine follow-up at 5 years of age and was confirmed to be pineoblastoma with subsequent biopsy; no tumor cells were noted in the cerebrospinal fluid or bone marrow. Following surgical debulking, this patient was treated with craniospinal radiation (36 Gy) with boost to the primary site (54Gy). This patient is currently 15 months from completion of therapy. For all patients on RET5, the median age at follow-up for 13q- patients is 5.6 years (range 3.4–11.1 years) and for non-13q- patients is 7.3 years (range 0.7–12.7 years); all patients are alive at last follow-up (median 6.1 years, range 7.6 months – 9.5 years).

Discussion

We identified 11 retinoblastoma patients with 13q- out of 105 patients (10%) treated on the same institutional protocol that had evidence of increased hematologic toxicity during chemoreduction therapy. When combined with an earlier report from SJCRH¹², the overall frequency of 13q- in patients with retinoblastoma was 6% (16 of 276), similar to previous reports.³ Therapy on a single prospective protocol ensured similar exposure to chemotherapy agents between patient groups as reported.

The only significant toxicity between groups was neutropenia leading to reduction of therapy more often in patients with 13q-. There is no region or gene located on the long arm of chromosome 13 (13q) that is known to play a role in hematopoiesis. Furthermore, in our 13q- population there were no overlapping regions of genes adjacent to the *RBI* deletions that could be targeted for further testing to find a common abnormality. Future functional testing and expression profile data of the specific regions deleted in 13q- patients (outside the *RBI* gene) may provide further clues to the etiology of their increased hematologic sensitivity.

Supportive care with GCSF was administered per protocol for topotecan exposure (Stratum B) and for all Stratum C patients receiving chemotherapy, but only for patients in Stratum A when delayed count recovery impacted planned chemotherapy. The numbers are too small for statistical comparison, but it is noted that 2/6 patients with 13q- required GCSF compared with 0/17 who did not have 13q- on Stratum A. Across all strata, more patients with 13q- had delays in therapy or chemotherapy dose reduction related to neutropenia than their non-13q- counterparts. Therefore, consideration of GCSF administration for supportive care in 13q- patients, regardless of chemotherapy regimen, is warranted.

13q- mosaicism has been reported in cases of retinoblastoma.^{18,19} One patient in our cohort had a sub-microscopic deletion of 13q in only 80% of the nuclei evaluated and had the fewest reported adverse events among all the 13q patients treated on the RET5 protocol. One meta-analysis indicates that mosaicism may not translate into a milder phenotype,²⁰ but it is unclear if 13q mosaicism has any impact on response to or toxicity with chemotherapy. With the advent of genome-wide screening, the frequency of the diagnosis of 13q- in retinoblastoma, including mosaicism, as well as our understanding of how mosaicism may impact patient outcomes may increase further.

Infectious complications (bacteremia or febrile neutropenia) and GI toxicity were similar between groups. GI deficiencies are a part of the 13q- spectrum.^{8,9} Cancer patients may struggle to maintain adequate nutrition without underlying GI abnormalities due to chemotherapy, so supportive care with prophylactic anti-emetics and intravenous fluids for symptomatic patients was provided as standard practice. In one 13q- patient, GI toxicity resulted in cessation of protocol therapy following one course of chemotherapy. This patient was noted to have concurrent constipation, raising the question of vincristine-related ileus as a component of the GI toxicity profile. Patients with 13q-, who are at risk for growth deficiencies may be more sensitive to the GI toxicities of chemotherapy, including vincristine-related neuropathy/ileus, and should be monitored closely for adequate bowel regimen, nutrition and growth.

Despite increased toxicity and delays or reductions in chemotherapy dosages, the response to therapy and overall survival were not different for 13q- patients compared with their counterparts. Therefore, aggressive supportive care and thoughtful consideration of reduction in therapy for retinoblastoma patients with 13q- provide acceptable disease outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported in part by American Lebanese Syrian Associated Charities (ALSAC), Research to Prevent Blindness, Inc., (NY), St Giles Foundation (NY), and National Institutes of Health grant numbers CA21765 and CA23099.

Financial support: none.

Thank you to Drs. Daniel Green and Alberto Pappo for editorial assistance and to Christine Odom for her work in genetic counseling for our patients.

Abbreviations Key

13q-	Deletion of the long arm (q) of chromosome 13
AEs	Adverse events
ANC	Absolute neutrophil count
EBRT	External beam radiation therapy
EOE	Extraorbital extension
FISH	Fluorescent in-situ hybridization
GCSF	Granulocyte colony stimulating factor
GI	Gastrointestinal
HR	High risk
HIPAA	Health Insurance Portability and Accountability Act
IR	Intermediate risk
IRB	Institutional Review Board
RB	Retinoblastoma
R-E	Reese-Ellsworth
SJCRH	St. Jude Children's Research Hospital
VC	vincristine/carboplatin
VCE	vincristine/carboplatin/etoposide
VCyD	vincristine/cyclophosphamide/doxorubicin
VT	vincristine/topotecan

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TABLE 1

Patient Characteristics for 68 Patients who received Chemotherapy by 13q Deletion Status

	13q Deletion		p value
	Yes (n=11)	No (n=57)	
Sex			0.51
Female	7 (64%)	27 (47%)	
Male	4 (36%)	30 (53%)	
Race			0.41 *
White	8 (73%)	41 (72%)	
Black	3 (27%)	8 (14.0%)	
Other	0 (0%)	8 (14.0%)	
Stratum			0.31 **
A	6 (55%)	17 (30%) ***	
B	2 (18%)	25 (44%)	
C – intermediate risk	2 (18%)	6 (11%)	
C – high risk	1 (9%)	9 (16%)	
Age at Diagnosis (months)			0.18
Median	9.6	7.3	
Range	3.2 – 27.3	0.4 – 71.4	

* white vs. black,

** A vs. B vs. C,

*** Percentages are rounded and may not sum to 100%.

TABLE 2

Grade 3 or 4 Neutropenia and Impact on Chemotherapy by 13q Deletion Status

	13q Deletion		p value
	Yes	No	
# of patients	11	57	
# (%) of patients with grade 3 or 4 neutropenia	11 (100%)	57 (100%)	>0.99 [^]
# (%) of patients with delayed chemotherapy due to neutropenia	9 (82%)	31 (54%)	0.11 [^]
# (%) of chemotherapy courses delayed due to neutropenia	18 (25%)	74 (16%)	0.35 [#]
# of patients with dose reduction due to neutropenia	5 (45%)	4 (7%)	<0.01 [^]
# of patients with dose reduction due to any reason	5 (45%)	6 (11%)	0.01 [^]

[^] Result based on Fisher's exact test[#] Result based on generalized estimating equation

TABLE 3

Numbers of Patients Experiencing Toxicity by 13q Deletion Status

	13q-				Normal				
Toxicity (Grade 3/4)	Stratum A (n=6)	Stratum B (n=2)	Stratum C (n=3)	TOTAL	Stratum A (n=17)	Stratum B (n=25)	Stratum C (n=15)	TOTAL	P value *
ANC	6	2	3	11 (100%)	17	25	15	57 (100%)	>0.99
Hgb	4	2	2	8 (73%)	6	21	12	39 (68%)	>0.99
Plt	3	2	1	6 (55%)	6	23	9	38 (67%)	0.50
ID	2	1	0	3 (27%)	1	18	3	22 (39%)	0.73
GI	3	2	0	5 (45%)	3	9	1	13 (23%)	0.14
VI-CN	1	0	0	1 (9%)	3	2	0	5 (9%)	>0.99
Drug	0	0	1 **	1 (9%)	2 ***	0	0	2 (4%)	0.42

ANC – Absolute Neutrophil Count; Hgb – Hemoglobin; Plt – Platelets; ID – Infectious Disease (bacteremia, fever/neutropenia); GI – Gastrointestinal (anorexia, dehydration, emesis); VI-CN – vincristine-induced cranial neuropathy (vocal cord paresis, aspiration, dysphagia, dysphonia) resulting in reduction or omission of vincristine therapy; Drug – drug reaction

* Comparison of specified toxicity for all 13q- patients vs. normal 13q status based on Fisher's exact test. Within-strata comparisons were not performed due to small numbers of patients.

** drug = etoposide,

*** drug = carboplatin (both patients)