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Features of regression of different stages of retinoblastoma after primary combined (intravitreal plus systemic) polychemotherapy and additional consolidation therapy

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Background: *Complete retinoblastoma (RB) regression is defined as final changes undergone by the tumor in the course of eye-salvage treatment. Studies of RB regression patterns following various types of eye-salvage treatment are important for assessing the outcomes of this treatment.*

Purpose: *To study the regression patterns in different stages of RB after primary combined polychemotherapy (PCPC) and additional consolidation therapy.*

Material and Methods: *We reviewed RB regression patterns in 89 children (119 eyes) aged 1.5 to 77 months after PCPC and various types of consolidation therapy. Of these children, 37 had unilateral retinoblastoma, and 52, bilateral retinoblastoma. At presentation, T3 RB (according to WHO lassification) was the most prevalent (67.2%), followed by T2 (23.6%). T1 stage was observed only in 9.2% - most often it was diagnosed on a fellow "healthy" eye at a spreading T3 stage of the countralateral eye. Sixteen eyes (13%) had multifocal type of tumor growth. Because the number of tumor foci per eye ranged from one to three, the total number of foci (124) exceeded the total number of affected eyes. Treatment was carried out according to the developed PCPC method, which invccluded the intravitral injection of melfalan at the dose of 10-30* μg, *depending on the tumor stage, followed by intravenous systemic therapy (VEC protocol).*

Results: *We found different RB regression patterns after PCPC. After the first cycle of PCPC, type 2 regression pattern was typical for small T1 tumors, whereas type 3 regression pattern was most prevalent (60%) for T2 and T3 tumors. This is likely to indicate tumor mosaicism with the presence of less differentiated and, consequently, more malignant cell types, which faster reacted to PCPC by calcification than surrounding more differentiated and, consequently, less malignant cells which reacted weaker. After the completion of PCPC, type 1 regression pattern was seen in 29%, which indicated complete regression, whereas type 3 regression pattern persisted in 33% foci. The features of tumor regression following PCPC included (a) fragmentation of a large RB (59.3%) after first 1-2 PCPC cycles with appearance of necrotic foci which resolved or calcified finally; (b) presence of various types of regression in one eye in the multifocal growth; and (c) transformation of a regression type into another regression type: most commonly, transformation of type 2 into type 3 and type 3 into type 1.*

Keywords:
retinoblastoma, eye-salvage treatment, chemotherapy

Introduction

Complete retinoblastoma (RB) regression is defined as final changes undergone by the tumor in the course of eye-salvage treatment. Dunphy [1], Ellsworth [2], Abramson and colleagues [3], Singh and colleagues [4] reported on regression of retinoblastoma lesions following radiation therapy, the earliest eye-salvage treatment. Subsequently, with the advent of other first-line treatment options (multiagent chemotherapy, laser therapy and brachytherapy), the types of tumor regression described by the above authors were confirmed [5-9].

Tumor regression patterns in retinoblastoma seen after conservative management include [3, 10, 11]:

Type 0 (complete disappearance with no remnant);

Type 1 (completely calcified tumor, as suggested by a “cottage cheese”–type texture);

Type 2 (a noncalcified tumor, as suggested by a gray, translucent appearance (ie, fish flesh regression));

Type 3 (a partially calcified tumor);

Type 4 (atrophy with a chorioretinal scar).

In 2010, Bobrova and Sorochynska [12] developed a new eye-salvage treatment option for retinoblastoma, the method of primary combined polychemotherapy (PCPC), a combination of intravitreal melphalan chemotherapy and

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systemic intravenous 3-drug (carboplatin, etoposide, and vincristine) chemoreduction.

The purpose of the study was to investigate the regression patterns in different stages of RB after PCPC and additional consolidation therapy.

Material and Methods

Eighty-nine children (119 eyes) with RB, aged from 1.5 months to 77 months, were treated at the Pediatric Ophthalmology Department. Of these children, 37 had unilateral retinoblastoma, and 52, bilateral retinoblastoma. The stages of the tumor at the primary examination were different: T3 RB was the most prevalent (67.2%) (Fig. 1a, 2a), followed by T2 (23.6%). T1 stage was observed rarely (9.2%); most often it was diagnosed on a fellow "healthy" eye at a spreading T3 stage of the countralateral eye

Sixteen eyes (13%) had multifocal type of growth. Because the number of tumor foci per eye ranged from one to three, the total number of foci (124) exceeded the total number of affected eyes.

The method of PCPC has been described by us previously [12]. In brief, melphalan was intravitreally injected at a dose of 10-30 µg [13], and the following day the child received systemic intravenous therapy. Totally, 119 eyes received 273 intravitreal injections, with the number of injections per eye ranging from 1 to 13 depending on tumor stage and pattern of RB regression. The number of cycles of systemic three-drug chemotherapy ranged from 1 to 6. Consolidation therapy (transpupillary thermotherapy (TTT), laser photocoagulation of tumor foci, cryotherapy and brachytherapy) was performed according to the methodologies developed [14, 15] in 67 eyes (78 foci) if indicated for final tumor regression.

Follow-up ranged from 17 to 125 months (mean plus or minus standard deviation, 60.69 ± 25.87 months) after final tumor regression.

Results

Three weeks after cycle 1 of PCPC, 106 eyes (89%) showed initial regression changes characterized by a decrease in prominence and change in tumor structure; the amount of decrease and severity of changes depended on the initial size of the tumor (Figs 1b, 2b). Considering the multifocal type of growth, the number of tumor foci with a positive response to PCPC (124) exceeded the total number of affected eyes.

In small T1 tumors, after cycle 1 of PCPC, type 2 regression pattern with or without change in focus size was seen most commonly (7/13 foci), followed by type 3 regression pattern (a grey, partially calcified tumor in 5/13 foci) and type 1 regression pattern (a completely calcified tumor in 1/13 foci). No case with type 0 or type 4 regression pattern was noted (Table 1). After the final cycle of PCPC in T1 tumors, type 0 regression pattern was noted in one case; types 1 and 2, in three cases each; type 3, in four cases; and type 4, in two cases.

In our opinion, types 2 and 3 regression patterns represented intermediate stages of the process, foci having these regression patterns were subject to subsequent consolidation therapy (laser therapy, cryotherapy or

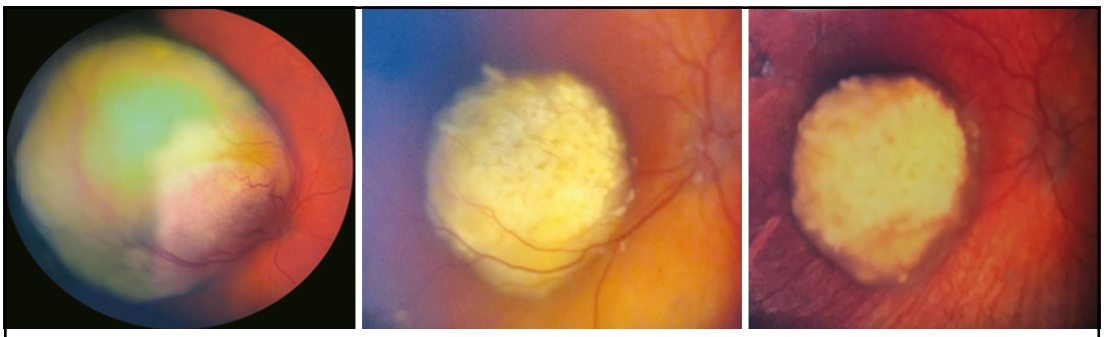

Fig. 1. T3b retinoblastoma: before treatment (A), regression to type 3 after cycle 1 of PCMC (B) and regression to type 3 after cycle 3 of PCMC.

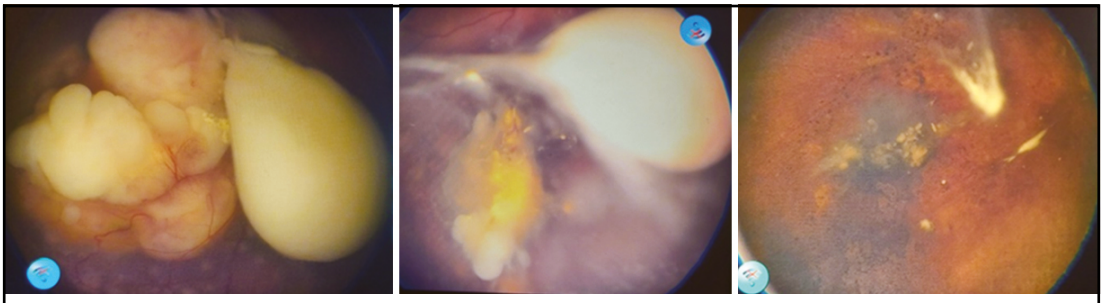

Fig. 2. T3a retinoblastoma with tumor capsule rupture and mass release into the vitreous: before treatment (A), regression to type 3 after cycle 1 of PCMC, detachment of large seeds from the initial site (B), and regression to type 1 after cycle 4 of PCMC and four intravitreal melphalan injections at a dose of 30 µg, with resolved and necrotic vitreous seeds

Table 1. Retinoblastoma (RB) regression patterns after the first cycle of PCMC

Regression patterns	RB stages						Total n (%)
	T1	T2	T3 (total)	T3a	T3b	T3c	
0	-	3	1	-	1	-	4 (3.2%)
I	1	6	4	-	2	-	11 (9%)
II	7	10	18	6	8	1	35 (28%)
III	5	15	54	10	28	1	74 (60%)
IV	-	-	-	-	-	-	-
Total, n (%)	13 (7%)	34 (19%)	77 (42%)	16 (9%)	39 (22%)	2 (1%)	124 (100%)

Note: PCMC, primary combination multiagent chemotherapy; n, number of patients

Table 2. Retinoblastoma (RB) regression patterns after the completion of PCMC

Regression patterns	RB stages						Total, n (%)
	T1	T2	T3 (total)	T3a	T3b	T3c	
0	1	3	2	-	1	-	6 (5%)
I	3	10	23	3	14	1	36 (29%)
II	3	5	18	3	9	1	26 (21%)
III	4	8	29	5	14	-	41 (33%)
IV	2	3	10	3	4	-	15 (12%)
Total, n (%)	13 (7%)	29 (16%)	82 (45%)	14 (8%)	42 (23%)	2 (1%)	124 (100%)

Note: PCMC, primary combination multiagent chemotherapy; n, number of patients

brachytherapy), which resulted in their regression to types 1 and 4 patterns, respectively (Table 3). Only in one case type 3 regression pattern did not change, and the condition of this tumor is still being monitored.

Therefore, after the first as well as the final cycle of PCPC, T1 tumors showed predominantly types 2 or 3 regression patterns, with type 3 pattern being more common than type 2 pattern after the final cycle of PCPC, and these tumors required consolidation therapy. This relative resistance of small tumors to intravitreal chemotherapy may be explained by the fact that they were most often located subretinally, whereas their resistance to systemic chemoreduction may be explained by the absence of tumor blood supply, which makes them low responsive to both components of PCPC.

Table 3. Retinoblastoma (RB) regression patterns after the completion of PCMC with adjuvant consolidation therapy

Regression patterns	RB stages						Total, n (%)
	T1	T2	T3 (total)	T3a	T3b	T3c	
0	-	3	1	-	1	-	4 (5%)
I	3	11	19	4	12	1	33 (42%)
II	-	-	1	-	-	-	1 (1%)
III	1	1	11	1	5	-	13 (17%)
IV	5	13	9	3	5	-	27 (35%)
Total, n (%)	9 (8%)	27 (25%)	40 (37%)	8 (7,5%)	22 (21%)	1 (1%)	78 (100%)

Note: PCMC, primary combination multiagent chemotherapy; n, number of patients

In T2 tumors, after cycle 1 of PCPC, type 3 regression pattern was observed most often (15/34 foci), followed by type 2 regression pattern (10/34 foci) and type 1 regression pattern (6/34 foci) (Table 1). Of note were three cases that reduced to type 0 regressions with complete traceless resorption of fresh endophytic foci in the presence of multifocal growth. Subsequent cycles of PCPC resulted in type 1 regression with complete calcification of most (10/29) foci, type 0 regression with complete resorption of 3/29 foci, and type 4 regression with flat chorioretinal atrophic scar in 3/29 foci. Intermediate regression types (types 2 and 3) were still seen 5/29 and 8/29 foci, respectively (Table 2). Consolidation therapy most often resulted in types 4 and 1 complete regression (13 and 11 foci, respectively). Two T2 tumors showed complete foci resorption and only one T2 tumor showed type 3 regression pattern and stayed under follow-up.

For large T3 tumors after the PCPC, the most characteristic was the development of type 3 regression (54/77 foci or 41.6%), followed by type 2 regression pattern (18/77 foci or 23.4%), whereas types 1 and 0 regression patterns were very uncommon (4/77 and 1/77 foci, respectively), and no T3 tumor with type 4 regression pattern was seen (Table 1). After the final cycle of PCPC, types 3 and 1 regression patterns were most common (29% and 23%, respectively; Figs 1C, 2C), the number of foci with type 2 regression patterns did not change (18 foci or 21.9%), type 4 appeared (10 foci or 12.2%), and 2 small foci (or 2.4%) completely resolved forming type 0. Of note was an increase in the number of foci in the course of treatment to 82 compared to 77 at baseline, which was caused by breakup of large tumors into smaller tumors and the appearance of new foci in the process of treatment.

Forty foci were subsequently subjected to consolidation therapy, which resulted in increases in the number of foci with type 1 regression pattern to 19/40 (42%) and with

type 4 regression pattern to 9/40 (35%). Twelve foci still have type 2 or, more commonly, type 3 regression patterns; they require continued follow-up and may require further treatment.

Therefore, the key feature of regression for large tumors after the first or the final cycle of PCMC was tumor fragmentation into smaller tumors (64 T2-T3 foci in 108 eyes; 59.3%). Most often, this was reflected in the decrease in size and increase in density of a large tumor focus and the appearance of numerous small retinal seeds in the presence of degenerative changes in the retina (Fig. 2c); subsequently, these seeds either resolved or calcified with treatment. In 12 cases, yellow necrotic areas appeared around the main focus. which, under the influence of further chemotherapy, were resolved or replaced by pigment.

In total, analyzing the reaction of 124 RB foci after the PCPC course, we noted that the tumor was most often reacted by type 3 regression pattern (60 %), followed by type 2 (28%) and type 1 (9%). The complete resorption of the tumor was very rare - in 4 cases (3.2%). The formation of type 4 regression pattern with chorioretinal scar formation was not observed.

After the final cycle of PCPC, in 124 RB foci, type 3 regression pattern (intermediate regression) was again the most common (41 or 33%), type 1 regression pattern increased in number (36 foci or 29%), type 2 regression pattern did not change in number (26 foci or 21%), type 4 regression pattern appeared (15 foci or 12%), and type 1 regression pattern with complete foci resorption increased in number (6 foci or 5%). Focal consolidation therapy resulted in types 1 and 4 regression patterns formation in 33/78 foci (42%) and 27/78 foci (35%), respectively, 4/78 foci (5%) completely resolved (type 0 regression patterns) and types 2 and 3 intermediate regression patterns were preserved in 1/78 foci (1%) and 13/78 foci (17%), respectively.

No regressive change after the first cycle of PCMC was observed in 13 eyes. These were eyes with large foci, high secondary RB-induced retinal detachment, and the presence of subretinal foci or multifocal growth. Although there were no signs of regression, we noted the stabilization of tumor growth, which required further treatment. Twelve eyes with T3 RB were enucleated after the completion of PCPC and consolidation therapy due to failure to achieve tumor regression with complete tumor control.

Discussion

The factors influencing retinoblastoma regression patterns have not been finally determined. However, initial tumor size was found to be a significant determinant of regression pattern. The distribution of RB regression types after external radiation therapy has established such pattern: type 1 regression pattern was seen in tumors of any size, but most often in large tumors; types 2 and 3 regression patterns were most often seen in medium-size and small foci, and type 0 regression pattern was seen only after treatment of tiny tumors. Ellsworth [2] reported that, type 1 was the most common regression pattern after radiation therapy for RB, whereas Abramson and colleagues [3] concluded that type 2 was the most common regression pattern. The authors also believe that type 1 regression pattern is typical for less differentiated and, correspondingly, more malignant cell types. In their opinion, type 2 regression pattern formed more differentiated and, consequently, less malignant tumor cell, which are less responsive to radiation. This type, according to the authors, is more cause anxiety of clinicians, because it appears as a rather active tumor.

Singh and colleagues [4] conducted a retrospective analysis of regression patterns following treatment of RB by external beam irradiation. There were 180 tumors in 104 eyes of 83 patients, 89% had bilateral disease, and 37%, a positive family history of RB. Type I regression was the commonest with 90 tumors (50%) assigned to this group. Types 0, II, and III were approximately equally distributed. In 21 tumors (25%) with Type II (eight) and Type III regression (13) the pattern changed with time. Type II regressed tumors converted mainly to Type 0 (six tumors) over a median interval of 22 months (range 5-33 months). Type III regressed tumors converted mainly to Type I (nine tumors), and Type 0 (three tumors). This conversion took place over a median interval of 27 months (range 6-83 months).

In the available literature, we have found a small number of work on the analysis of RB regressin models after PCT and consolidating therapy and no work described the regression of the RB after primary local chemotherapy, since intravitreal injections of cytostatic Melphalan are not used as such treatmet mode in other centers. Chawla and colleagues (2012) [16] studied the regression patterns of early retinoblastoma (Groups A and B, according to the International Classification System) after systemic chemotherapy and focal consolidation. The most common regression pattern noted in their study was type 4 (50.2%), followed by type 3 (31.7%). Shields et al. [11] and Palamar et al (2011) [17] reported a comparable frequency of Type 4 and Type 3 regression patterns (33% and 32%, respectively). Those studies also included advanced Group C and Group D tumors. Similar findings were reported by Zafar and colleagues (2016) [18], with type 4 regression and type 3 regression seen in 39.1% and 25.1% of 74 tumors of groups A to D. In another series of 100 RB tumors in 57 eyes of 35 patients treated with systemic chemoreduction and focal therapy, type 3 was reported to be the predominant pattern of regression after treatment [19]. In a Chinese series [20] of 122 RB tumors in 47 eyes (groups A-D) of 37 children treated with combined chemoreduction (VEC) and adjuvant therapy (cryotherapy and/or TTT), type 4 was reported to be the predominant pattern of regression after treatment. In addition, tumor thickness and tumor location were related to regression patterns. Tumors with an initial thickness of 2 mm or less regressed most often to type 4, and those thicker than 8 mm regressed to type 1 or type 3. Tumors with greater distance from the foveola regressed most often to type 4.

A high rate of type 4 regression in some foreign studies is likely to be explained by earlier and wide prescription of consolidation therapy.

Type 1 regression pattern was seen after the final cycle of PCMC in all RB stages. The use of additional consolidation therapy allowed for complete regression with type 1 regression pattern (completely calcified remnant) or type 4 regression pattern (atrophic chorioretinal scar) in all RB stages.

In the current study, we observed different regression patterns in a series of 124 RB foci in 119 eyes of 89 children after PCPC. After the first cycle of PCPC, type 1 2 regression pattern was typical for small T1 tumors, whereas type 3 (intermediate) regression pattern was most prevalent (60%) for T2 and T3 tumors. This is likely to indicate tumor mosaicism with the presence of less differentiated and, consequently, more malignant cell types, which faster reacted to PCPC by calcification than surrounding more differentiated and, consequently, less malignant cells which reacted weaker. After the completion of PCMC, type 1 regression pattern was seen in 29%, which indicated complete regression, whereas type 3 regression pattern persisted in 33% of RB foci.

Conclusion

The features of tumor regression following PCPC included (a) fragmentation of a large RB (59.3%) after first 1-2 PCPC cycles with appearance of necrotic foci which resolved or calcified finally; (b) presence of various types of regression in one eye in the multifocal growth; and (c) transformation of a regression type into another regression type: most commonly, transformation of type 2 into type 3 and type 3 into type 1.

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Disclosures

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