NEURO-SIGNALS

Neurosignals 2021;29(S1):1-7
DOI: 10.33594/000000367
Published online: 5 May 2021
Accepted: 2 April 2021

www.neuro-signals.com

Original Paper

Primary Vitreoretinal Lymphoma Therapy Monitoring: Significant Vitreous Haze Reduction After Intravitreal Rituximab

Vinodh Kakkassery[a,b] Ludwig M. Heindl[c,d] Alexander C. Rokohl[c] Arygrios Chronopoulos[e] James S. Schutz[e] Mahdy Ranjbar[a] Marc Schargus[b,f,g] Alexander Böker[h,i] Sibylle Winterhalter[h,i] Nicole Stübiger[h,i,j]

[a]Department of Ophthalmology, University of Lübeck, Lübeck, Germany, [b]Department of Ophthalmology, Ruhr-University, Bochum, Germany, [c]Department of Ophthalmology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany, [d]Center for Integrated Oncology (CIO) Aachen-Bonn-Cologne-Duesseldorf, Cologne, Germany, [e]Department of Ophthalmology, Klinikum Ludwigshafen, Ludwigshafen, Germany, [f]Department of Ophthalmology, Heinrich-Heine-University, Düsseldorf, Germany, [g]Department of Ophthalmology, Asklepios Hospital Nord-Heidberg, Hamburg, Germany, [h]Department of Ophthalmology, Charité – University Medicine Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany, [i]Berlin Institute of Health, Berlin, Germany, [j]Department of Ophthalmology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Key Words
Primary vitreoretinal lymphoma • Central nervous system lymphoma • Rituximab • Therapy • Vitreous haze • Tumour regression • Intraocular safety

Abstract
Background/Aims: Intravitreal rituximab is an off-label treatment option for primary vitreoretinal lymphoma (PVRL). The objective of this study was to monitor the therapeutic response and safety profile of intravitreal rituximab in a cohort of PVRL patients. ***Methods:*** In this retrospective, uncontrolled, open label, multicentre study, 20 eyes from 15 consecutive patients diagnosed with PRVL received at least one intravitreal injection of 1mg in 0.1ml rituximab. Biodata of the PVRL patients was recorded as well as visual acuity and vitreous haze score immediately before rituximab intravitreal injection and at follow-up examinations. Intravitreal rituximab safety data was also recorded. Additional rituximab injections were made during control visits on a pro re nata (PRN) regime using increased vitreous haze to indicate recurrence. ***Results:*** There was significant vitreous haze reduction (p=0.0002) followed by significant improvement of visual acuity (mean best visual acuity before therapy 0.57 logMAR, after therapy 0.20 logMAR (p=0.0228) during the follow-up time up to 4 years. Only mild

Vinodh Kakkassery, MD
Department of Ophthalmology, UKSH, University of Lübeck,
Ratzeburger Allee 160, 23538 Lübeck (Germany)
Tel. +49 451 500 43911, Fax +49 451 500 43914, E-Mail vinodh.kakkassery@gmail.com

ocular side effects were reported. Median follow-up time was 565 days (range, 7-1253 days). ***Conclusion:*** Intravitreal rituximab therapy shows promising PVRL regression without any severe side effects. Although our clinical data support rituximab as intravitreal therapy in PVRL disease, further study is warranted.

Introduction

Primary vitreoretinal lymphoma (PVRL) is a rare malignant lymphoma manifesting in the eye. Incidence has been estimated at less than 0.5 cases per 100.000 per year [1]. PRVL occurs in 15 to 25% of primary CNS lymphoma patients [2]. Conversely, 65 to 90% of PVRL patients develop primary CNS lymphoma (PCNSL). PVRL implicates a considerably reduced overall survival [3].

To date, according to the international primary central nervous system lymphoma collaborative group (IPCG), state of the art PVRL treatment is intravitreal chemotherapy in isolated eye disease or a combination of intravitreal and systemic chemotherapy, the later mandated when central nervous system involvement is present [1, 4].

Rituximab (RTX) is an anti-CD20 antibody and was approved treatment of choice by FDA in 1997 for non-Hodgkin's B-cell lymphoma and subsequently for diffuse large B-cell lymphoma [5-7]. At present, RTX is used systemically in combination with conventional chemotherapy in CD20-positive lymphomas and demonstrates better overall survival as well as better disease-free survival than isolated conventional chemotherapy [8]. Intravitreal RTX has already demonstrated favourable disease regression in PVRL in small case series without any severe ocular or systemic side effects, in particular, no corneal or retinal toxicity [9-11]. However, intravitreal rituximab therapy is still considered an orphan disease off-label treatment for PVRL.

In order to further establish efficacy and safety of intravitreal rituximab therapy, the objective of this study was to analyse visual acuity and vitreous haze as a measure of intraocular tumour burden before and after intravitreal pro re nata (PRN) rituximab treatment [1]. A secondary objective was to monitor side effects to assess the safety of this therapy.

Materials and Methods

Study design

This study was performed as a retrospective, uncontrolled, open label analysis. Data from patients with PVRL who received intravitreal rituximab between 2007 and 2015 were retrospectively analysed. Ruhr-University ethics committee approval (Register no 15-5557, Bochum, Germany) was obtained for retrospective analysis. The study was conducted following the tenets of the Helsinki declaration as well as its later amendments.

Patient biodata

PVRL patient data were collected from 4 centres (5 patients/8 eyes University Hospital Bochum, 5 patients/5 eyes University Hospital Cologne, 4 patients/6 eyes Charité University Hospital Berlin, 1 patient/1 eye University Hospital Würzburg) for a total of 15 patients and 20 eyes included in the study. PVRL patient characteristics as well as demographic data were recorded including age of diagnosis, gender, eye laterality, PCNSL manifestation during observational time and HIV status, and are summarized in Table 1.

RTX treatment procedure in PVRL patients

Intravitreal injection of 1mg RTX in 0.1mL was performed in accordance with the German Ophthalmic Society guidelines for intravitreal injections. First treatment was conducted following diagnosis of PVRL. Further treatments were performed at monthly controls depending on vitreous haze status as a measure of PVRL vitreous burden using the Nussenblatt standardisation of uveitis nomenclature classification [12-14].

Further RTX injections were made during each control visit based if vitreous haze was not decreased. No other medication was given during the follow-up unless CNS involvement occurred. Ophthalmic recurrence was defined by any increased vitreous haze from follow-up timepoint to follow-up timepoint and CNS recurrence was defined by a haemato-oncologist.

Intravitreal RTX ocular tumour control data recording

Best logMAR visual acuity, vitreous haze measurement by the Nussenblatt uveitis classification scale, observation time duration and duration without intravitreal therapy were recorded during follow-ups. Ocular therapy success was based on by best visual acuity and vitreous haze. Five experienced, independent examiners, who did not treat patients in the study, graded the Nussenblatt vitreous haze uveitis score before and throughout the study.

Intravitreal RTX safety data recording

Patients' data files were scanned for ocular recurrence or any ocular adverse effects during scheduled clinical visits; ocular and systemic side effects and possible complications of therapy were recorded.

Statistical analysis

Statistical analysis was performed for logMAR best visual acuity and vitreous haze score comparing pre- and post-treatment results. Data is presented as mean ±SD ±SEM unless otherwise stated. Pre- and post-treatment results were compared by ANOVA followed by Tukey post-hoc testing using Statistical Software (V10.0, Statsoft, Tulsa, Ok, USA). P-values below 0.05 were considered statistically significant.

Table 1. Biodata: PVRL patients' parameter. Biodata as well as clinical parameters for intravitreal rituximab treatment are noted for all 20 eyes from 15 PVRL patients. Eye (RE=right eye; LE=left eye), gender (m=male), adverse effects (0=not described), ocular side effects (0=not described, 1=elevated intraocular pressure; 2=cataract; 3=retinal detachment), diagnosis (0=unknown, 1=vitreous biopsy, 2=CNS, 3=clinical diagnosis; 4=retinal biopsy), PCNSL (0=no CNS lymphoma, 1=CNS lymphoma), HIV (0=no, 1=yes), vitrectomy before treatment (0=no vitrectomy before treatment, 1= vitrectomy before treatment), MTX=methotrexate, BCNN/TT=carnemustine/thiotepa

Eye No.	Patient No.	Eye	Gender	Age at diagnosis [years]	Number of injections	Observation time [days]	Time duration w/o therapy [days]	Adverse effects	Ocular side effects	Diagnosis	PCNSL	HIV	Vitrectomy before treatment	Further PVRL/PCNSL treatment
1	1	LE	f	66	1	982	35	0	0	2	1	2	1	intrathecal MTX
2	2	RE	m	70	1	353	359	0	2	4	0	0	1	-
3	2	LE	m	70	1	353	359	0	2	4	0	0	1	-
4	3	RE	m	51	7	677	546	0	0	3	1	0	0	unknown systemic chemotherapy before intravitreal therapy
5	3	LE	m	51	5	677	546	0	0	3	1	0	0	unknown systemic chemotherapy before intravitreal therapy
6	4	RE	f	71	3	307	10	0	1+2+3	1	0	0	0	-
7	4	LE	f	71	4	307	10	0	1+2+3	1	0	0	0	-
8	5	LE	f	80	0	7	1	0	0	1	0	2	0	-
9	6	RE	f	67	0	196	90	0	3	3	1	0	1	-
10	7	LE	m	75	1	383	383	0	0	1	1	0	0	percutaneous ocular irradiation
11	8	RE	m	79	2	602	547	0	0	1	1	0	0	7 x rituximab, 3 x Temozolomid
12	8	LE	m	77	1	1050	271	0	0	1	1	0	1	8 x rituximab, 3 x temozolomide, 4 x MTX, cytarabine, 3 x ifosfamide
13	9	LE	f	69	3	237	32	0	0	1	0	0	0	CNS lymphoma & systemic chemo-therapy after tumor control
14	10	RE	f	72	1	1253	947	0	0	3	0	0	0	4 x MTX intravitreal, 3x ifosfamid/rituximab, 1 x high-dose MTX, 1 x HD BCNU/TT, state after stem cell tx
15	10	LE	f	72	1	1253	833	0	0	1	0	0	1	1 x MTX intravitreal, 3x ifosfamide/rituximab, 1x high-dose MTX, 1x HD BCNU/TT Cycle, state after stem cell tx
16	11	RE	m	43	3	143	40	0	0	1	1	0	1	3 x ifosfamid/rituximab
17	12	LE	w	72	3	580	242	0	0	1	0	2	1	6 x rituximab
18	13	RE	m	77	2	689	379	0	0	1	0	0	1	6 x rituximab
19	14	LE	w	73	1	550	96	0	0	4	0	0	1	8 x rituximab
20	15	RE	w	73	2	806	169	0	0	1	1	0	1	8 x rituximab

PVRL registry implementation

Relevant data was recorded in a nationwide open registry for PVRL (http://www.lymphome.de/Gruppen/G-PCNSL-SG/Protokolle/index.jsp) supported by the German Federal Ministry of Education and Research.

Results

Biodata

20 eyes (9 right eyes/11 left eyes) from 15 PVRL patients (6 male/9 female) were included in this study. Mean age at diagnosis was 72 years (range, 43-80 years). Follow-up median time was 565 days (range, 7-1253 days). Follow-up median time after last treatment was 257 days (range, 1-947 days). 7 patients had concurrent PCNSL at the time of diagnosis. During study follow-up, no additional PCNSL case was detected. PVRL diagnosis was established by vitreous biopsy in 12 eyes (23g pars plana vitrectomy), by retinal biopsy in 3 eyes, and by clinical diagnosis in 5 eyes, one of which with PCNSL confirmed by brain biopsy. HIV simultaneous infection was ruled out by serology testing in all but 3 patients who declined testing. Complete vitrectomy was performed in 11 eyes before treatment. Previous systemic therapy for PCNSL was performed in 11 patients before intravitreal RTX treatment.

Intravitreal rituximab ocular lymphoma control data recording

20 eyes were treated with intravitreal rituximab following a PRN regime. An average of 2 injections (range from 1-7) were performed in each treated eye. Macular photographs of three exemplary patients are shown before starting and after ending intravitreal rituximab therapy in Fig. 1.

Visual acuity after intravitreal RTX

Mean visual acuity before therapy was 0.57+/- 0.57 logMAR (decimal 0.25 - metric 6/24) with a SEM +/- 0.13. Mean visual acuity after therapy increased to 0.20+/- 0.41 logMAR (decimal 0.63 - metric 6/9.5) with a SEM +/- 0.09, statistically significant (p=0.02). Box plots demonstrate mean values for visual acuity as well as SEM and statistical significance between before and after treatment in Fig. 2a.

Ocular tumour control after intravitreal RTX

Mean vitreous haze score before therapy was graded as +2 with a standard deviation of +/- 0.85 (SEM +/- 0.19). Mean vitreous haze score after therapy decreased to grade 0 with a standard deviation of +/- 0.88 (SEM +/- 0.20), statistically significant (p=0.0002). Box plots demonstrate mean values for vitreous haze score as well as SEM and statistical significance throughout the study in Fig. 2b.

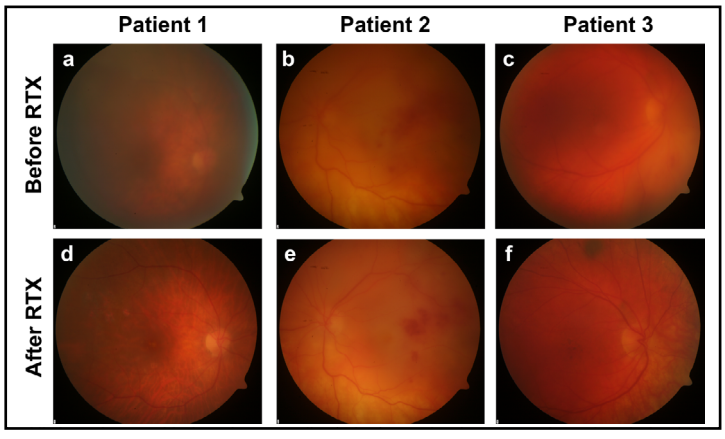

Fig. 1. Example of fundus series before/after rituximab. All 3 patients with lymphoma cells (a,b,c) received up to 7 intravitreal rituximab injections and had reduced vitreous haze scores afterwards (d,e,f).

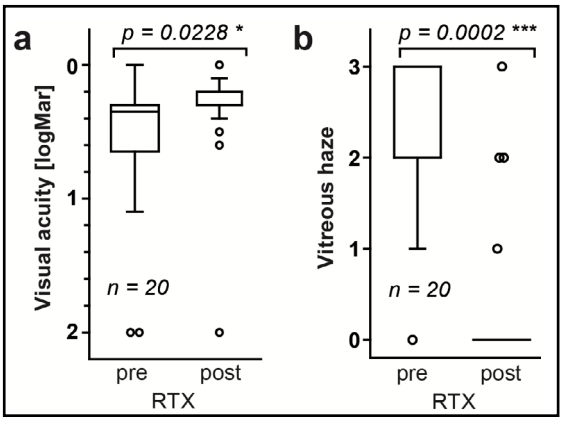

Fig.2 a) Boxplot of logMAR visual acuity before treatment and after treatment, b) Boxplot of vitreous haze score before treatment and after treatment. a) Mean visual acuity before therapy was logMAR 0.57 logMAR with a standard deviation of +/- 0.57 (SEM +/- 0.13). Mean visual acuity after therapy increased to 0.20 logMAR, significant (p=0.02). b) Mean vitreous haze score before therapy was graded +2 with a standard deviation of +/- 0.85 (SEM +/- 0.19). Mean vitreous haze score after therapy decreased to grade 0 with a standard deviation of +/- 0.88 (SEM +/- 0.20), significant (p=0.0002).

Intravitreal rituximab safety data recording

In one patient, both treated eyes developed temporary intraocular pressure increase as well as a tumour related exudative retinal detachment with intraocular bleeding. No further treatment was needed because both the increased intraocular pressure and exudative retinal detachment with intraocular bleeding resolved spontaneously. The same eyes developed cataract which did not require surgery during follow-up. One additional patient developed self-limiting tumour-related exudative retinal detachment and one patient developed bilateral cataract not requiring surgery during the follow-up. No other ocular or systemic adverse effect was reported.

Discussion

In our retrospective study, intravitreal RTX treatment produced impressive intraocular lymphoma cell reduction in PVRL patients. No other intravitreal or systemic was given during the treatment period. Vitreous haze score was reduced significantly and best visual acuity was increased significantly after treatment. Based on our data, we conclude that RTX is effective and well tolerated as intravitreal PVRL treatment with a low rate of side effects. Temporary increased intraocular pressure as well as a tumour related exudative retinal detachment with intraocular bleeding was seen in both eyes of one patient; one patient developed self-limiting tumour related exudative retinal detachment and one patient developed bilateral cataract not requiring surgery during the follow-up. No other ocular or systemic adverse effect was reported.

Previously, PVRL treatments included systemic chemotherapy, beam radiation or intravitreal methotrexate [1, 15-17]. Systemic therapy is usually associated with severe side effects. Beam radiation leads to radiation retinopathy. Intravitreal methotrexate may cause irreversible corneal and retinal toxic effects [1, 12]. Therefore, interest in targeted intravitreal treatment that could avoid these complications is high. The first intravitreal application of RTX in the treatment of PVRL was reported by Kitzmann et al. in 2007 followed by Ohguro et al. in 2008 [9, 18]. Kitzmann treated with intravitreal RTX 8 eyes from 5 PVRL patients with up to 4 intravitreal injections and reported successful reduction of measured parameters, particularly improvement of vitreous haze and visual acuity, without any side effects. Ohguro treated 3 eyes from 2 patients which developed PVRL recurrence after intravitreal methotrexate with up to 2 intravitreal RTX injections/eye. A gross reduction of vitreous haze score occurred in all eyes, but visual acuity results were not reported. In a subsequent multicentre retrospective study, Larkin et al. reported 48 eyes from 34 PVRL patients of whom 37 patients were treated with RTX only and 11 with a combination of RTX and methotrexate [11]. Treatment regime differed from centre to centre between strict injection regime or PRN regime. The most common treatment interval was monthly with a median of 4 injections.

Remission occurred in 65% of eyes with increased visual acuity after treatment but ocular side effects included cataract (19%), elevated intraocular pressure (4%), granulomatous anterior uveitis (2%), vitreous haemorrhage (2%), and rhegmatogenous retinal detachment (2%). Hashida et al. reported promising results in a one-year-study of 20 PVRL eyes from 13 women previously treated with intravitreal methotrexate which was stopped because of corneal epitheliopathy [10]. Visual acuity was not reported. All these studies reported no permanent ocular or systemic side effects from RTX.

In contrast to these studies, we measured vitreous haze score in a standardized manner and also performed statistical analysis for visual acuity and vitreous haze score. In our study, intraocular pressure increase, tumour related retinal detachment and cataract was seen in some patients. Temporary intraocular pressure increase has been seen in patients with intravitreal injection for other diseases like age-related macular degeneration and diabetic macular oedema, probably related to the intravitreal injection procedure and rather to RTX itself. Tumour related retinal detachment but not rhegmatogenous retinal detachment is an occasional feature of PVRL [1].

Our study has limitations. Our analysis was performed retrospectively and the number of PVRL patients investigated was low because of the relative rarity of this disease [1, 12-14]. The vitreous haze score used to measure the PVRL status is a useful but relatively crude clinical measure of intraocular lymphoma activity. Evaluation of interleukin 10/6 ratio in the aqueous humour or microRNA 92, 19b and 21 in the vitreous space might be more accurate for monitoring PVRL therapy in the future [1, 10, 19, 20].

Conclusion

There is still no gold standard treatment for PVRL. This pilot study demonstrates a statistically significant reduction of vitreous haze score and improvement of visual acuity following PRN treatment with intravitreal RTX. Our results support intravitreal RTX treatment in patients with PVRL as sole treatment. Further testing in larger cohorts is needed to better establish treatment criteria. Discovery of biomarkers for therapy monitoring also might improve the validation of PVRL tumour control.

Acknowledgements

Author Contributions

Conceptualization, V.K. and N.S.; methodology, V.K., L.M.H, S.W and N.S.; software, A.C.R, A.C., M.S.; validation, V.K. and N.S.; formal analysis, M.R. and J.S.S.; investigation, V.K., L.M.H., A.C.R, A.B., M.S., S.W. and N.S.; resources, V.K. and N.S.; data curation, M.R. and J.S.S.; writing—original draft preparation, V.K., J.S.S., N.S.; writing—review and editing, L.M.H., A.C.R., A.C., M.R., M.S., A.B. and S.W.;visualization, V.K., A.C., M.R.; supervision, V.K. and N.S.; project administration, V.K. and N.S.; funding acquisition, V.K. and N.S.. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Disclosure Statement

The authors declare no conflicts of interest exist.

References

1 Chan CC, Rubenstein JL, Coupland SE, Davis JL, Harbour JW, Johnston PB, Cassoux N, Touitou V, Smith JR, Batchelor TT, Pulido JS: Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. Oncologist 2011;16:1589-1599.
2 Hochberg FH, Miller DC: Primary central nervous system lymphoma. J Neurosurg 1988;68:835-853.
3 Coupland SE, Heimann H, Bechrakis NE: Primary intraocular lymphoma: a review of the clinical, histopathological and molecular biological features. Graefes Arch Clin Exp Ophthalmol 2004;242:901-913.
4 Riemens A, Bromberg J, Touitou V, Sobolewska B, Missotten T, Baarsma S, Hoyng C, Cordero-Coma M, Tomkins-Netzer O, Rozalski A, Tugal-Tutkun I, Guex-Crosier Y, Los LI, Bollemeijer JG, Nolan A, Pawade J, Willermain F, Bodaghi B, ten Dam-van Loon N, Dick A, et al.: Treatment strategies in primary vitreoretinal lymphoma: a 17-center European collaborative study. JAMA Ophthalmol 2015;133:191-197.
5 Anderson DR, Grillo-Lopez A, Varns C, Chambers KS, Hanna N: Targeted anti-cancer therapy using rituximab, a chimaeric anti-CD20 antibody (IDEC-C2B8) in the treatment of non-Hodgkin's B-cell lymphoma. Biochem Soc Trans 1997;25:705-708.
6 Coiffier B, Haioun C, Ketterer N, Engert A, Tilly H, Ma D, Johnson P, Lister A, Feuring-Buske M, Radford JA, Capdeville R, Diehl V, Reyes F: Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood 1998;92:1927-1932.
7 Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P, Gisselbrecht C: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235-242.
8 Friedberg JW, Kim H, McCauley M, Hessel EM, Sims P, Fisher DC, Nadler LM, Coffman RL, Freedman AS: Combination immunotherapy with a CpG oligonucleotide (1018 ISS) and rituximab in patients with non-Hodgkin lymphoma: increased interferon-alpha/beta-inducible gene expression, without significant toxicity. Blood 2005;105:489-495.
9 Kitzmann AS, Pulido JS, Mohney BG, Baratz KH, Grube T, Marler RJ, Donaldson MJ, O'Neill BP, Johnston PB, Johnson KM, Dixon LE, Salomao DR, Cameron JD: Intraocular use of rituximab. Eye 2007;21:1524-1527.
10 Hashida N, Ohguro N, Nishida K: Efficacy and Complications of Intravitreal Rituximab Injection for Treating Primary Vitreoretinal Lymphoma. Transl Vis Sci Technol 2012;1:1.
11 Larkin KL, Saboo US, Comer GM, Forooghian F, Mackensen F, Merrill P, Sen HN, Singh A, Essex RW, Lake S, Lim LL, Vasconcelos-Santos DV, Foster CS, Wilson DJ, Smith JR: Use of intravitreal rituximab for treatment of vitreoretinal lymphoma. Br J Ophthalmol 2014;98:99-103.
12 Nussenblatt RB, Palestine AG, Chan CC, Roberge F: Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology 1985;92:467-471.
13 Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature Working G: Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005;140:509-516.
14 Oliver GF, Stathis RM, Spurrier NJ, Smith JR: Use of Standardization of Uveitis Nomenclature for Reporting Clinical Data at 10 Years. Ophthalmology 2017;124:1084-1085.
15 Batchelor TT: Primary central nervous system lymphoma: A curable disease. Hematol Oncol 2019;37:15-18.
16 de Smet MD, Vancs VS, Kohler D, Solomon D, Chan CC: Intravitreal chemotherapy for the treatment of recurrent intraocular lymphoma. Br J Ophthalmol 1999;83:448-451.
17 de Smet MD: Management of non Hodgkin's intraocular lymphoma with intravitreal methotrexate. Bull Soc Belge Ophtalmol 2001:91-95.
18 Ohguro N, Hashida N, Tano Y: Effect of intravitreous rituximab injections in patients with recurrent ocular lesions associated with central nervous system lymphoma. Arch Ophthalmol 2008;126:1002-1003.
19 Raja H, Snyder MR, Johnston PB, O'Neill BP, Caraballo JN, Balsanek JG, Peters BE, Decker PA, Pulido JS: Effect of intravitreal methotrexate and rituximab on interleukin-10 levels in aqueous humor of treated eyes with vitreoretinal lymphoma. PLoS One 2013;8:e65627.
20 Kakkassery V, Schroers R, Coupland SE, Wunderlich MI, Schargus M, Heinz C, Wasmuth S, Heiligenhaus A, Ahle G, Lenoble P, Schlegel U, Schmiegel W, Dick HB, Baraniskin A: Vitreous microRNA levels as diagnostic biomarkers for vitreoretinal lymphoma. Blood 2017;129:3130-3133.