

**TO THE EDITOR:**

# Temozolomide is effective and well tolerated in patients with primary vitreoretinal lymphoma

Marine Baron,<sup>1</sup> Lisa Belin,<sup>2</sup> Nathalie Cassoux,<sup>3</sup> Christine Fardeau,<sup>4</sup> Marion Blaizeau,<sup>5</sup> Carole Soussain,<sup>6</sup> Caroline Houillier,<sup>7</sup> Khê Hoang-Xuan,<sup>7</sup> Emmanuel Gyan,<sup>8</sup> Marie-Laure Le Lez,<sup>9</sup> Anne Lavaud,<sup>1</sup> Pierre Soubeyran,<sup>10</sup> Bahram Bodaghi,<sup>4</sup> Myrto Costopoulos,<sup>11</sup> Véronique Leblond,<sup>1</sup> Valérie Toutou,<sup>4</sup> Karim Maloum,<sup>11</sup> Marie-Hélène Errera,<sup>12</sup> Damien Roos-Weil,<sup>1</sup> Magali Le Garff-Tavemier,<sup>11</sup> and Sylvain Choquet<sup>1</sup>

<sup>1</sup>Sorbonne Université, Service d'Hématologie Clinique, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France; <sup>2</sup>Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Unité Mixte de Recherche (UMR) 1136, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Service de Biostatistiques, Santé Publique et Informatique Médicale, Centre d'Investigation Clinique (CIC) 1421, Paris, France; <sup>3</sup>Service d'Oncologie Oculaire, Faculté de Médecine René Descartes Paris V, Paris, France; <sup>4</sup>Sorbonne Université, Service d'Ophtalmologie, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France; <sup>5</sup>Service d'Ophtalmologie, Centre Hospitalo-Universitaire de Bordeaux, Bordeaux, France; <sup>6</sup>Service d'Hématologie Clinique, Institut Curie, Saint Cloud, France; <sup>7</sup>Sorbonne Université Service de Neuro-Oncologie, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France; <sup>8</sup>Service d'Hématologie et de Thérapie Cellulaire, and <sup>9</sup>Service d'Ophtalmologie, Centre Hospitalier Régional Universitaire de Tours, Tours, France; <sup>10</sup>Service d'Oncologie, Institut Bergonié, Bordeaux, France; <sup>11</sup>Sorbonne Université, Service d'Hématologie Biologique, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France; and <sup>12</sup>Service d'Ophtalmologie, Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts, Paris, France

Primary vitreoretinal lymphoma (PVRL) is a rare non-Hodgkin lymphoma, frequently associated with primary central nervous system (CNS) lymphoma (PCNSL).<sup>1</sup> It particularly concerns elderly subjects with limitations to receive chemotherapies. The prognosis is poor due to the risk of CNS involvement. Between 60% and 85% of patients will develop CNS localization within 29 months.<sup>2</sup> Publications on subsequent treatments are scarce. Temozolomide (TMZ) is a well-tolerated, second-generation alkylating agent with excellent penetration into the CNS and the cerebrospinal fluid (CSF). Its activity in PCNSL has been demonstrated in small studies,<sup>3-6</sup> but never in PVRL. Here, we present the results of a retrospective, multicentric study evaluating the efficacy and safety of TMZ as treatment of relapsed or refractory (R/R) patients or in patients not eligible for intensive treatment in first line.

Adults with R/R PVRL or not eligible for intensive treatments were treated with TMZ orally at a dose of 150 mg or 200 mg/m<sup>2</sup>, 5 days a month, every month. TMZ was proposed through the French National Lymphome Oculo-Cérébral (LOC) network, which brings together experts on PVRL and gives therapeutic guidelines. In accordance with the Declaration of Helsinki, the study was approved by the LOC network institutional review board. The diagnosis of PVRL was made by cytological examination and staining with anti-CD3, anti-CD20, and anti-CD79b antibodies of vitrectomy material or by histological examination of cerebral biopsy in case of associated brain lesions. Interleukin (IL)-10 and IL-6 assays were performed on the vitreous and/ or the aqueous humor (AH) using the Cytometric Bead Array (CBA) technique.<sup>7</sup> The IL Score for intraOcular Lymphoma Diagnosis (ISOLD), with a published sensitivity and specificity of 93% and 95%, respectively, was used.<sup>7</sup> According to the literature, an ISOLD score >4.6 in vitreous or AH has a 99% probability of PVRL. Clonality assay was performed on the vitreous by multiplex polymerase chain reaction-based analysis of immunoglobulin heavy and light chain gene rearrangements following the BIOMED-2 protocol.<sup>8</sup> Patients underwent gadolinium magnetic

resonance imaging (MRI), lumbar puncture, and positron emission tomography or computed tomography scan. CSF was analyzed by cytology, flow cytometry, clonality, and IL-10 and IL-6 assays when possible. Responses were evaluated by ophthalmological examination, supplemented by gadolinium MRI in the case of associated brain lesions, according to International Primary CNS Lymphoma Collaborative Group criteria.<sup>9</sup> IL levels were measured periodically in the AH during the follow-up of some patients. Survival functions and median survivals were estimated using the Kaplan-Meier method, and survival rates and 95% confidence intervals (CIs) were calculated using Greenwood variance.

Twenty-one patients were included. Median age was 75 years (range, 35-90 years), 1 patient had associated brain localization, and all patients tested for CSF were negative. Nine patients had received 1 line of treatment before, 7 patients 2 lines, 2 patients 3 lines, and 1 patient 4 lines. Two patients, aged 85 and 90 years, had never been treated before. Anterior lines treatments contained high-dose (HD) methotrexate (MTX) for 14 patients. The remaining 5 patients had received HD cytarabine (n = 3) or intravitreal injections of MTX (n = 2). Two patients had received an autologous stem cell transplant (ASCT), and 1 patient cerebral radiotherapy prior to TMZ. One patient with cerebral localization was refractory to lenalidomide, and 2 patients were refractory to ibrutinib. Median duration of treatment with TMZ was 5.2 months (range, 1-40 months). Patients' therapeutic history is summarized in Table 1.

B-cell clonality was positive in 14 out of 15 tested patients. In the single patient with a negative search for clonality, the diagnosis was confirmed by cytological test and antibodies, and the IL-10/IL-6 ratio was 30. Median IL-10 concentration in the vitreous was 1805 pg/mL (range, 346-5000 pg/mL). IL-10/IL-6 ratio was >1 in the 13 tested patients (range, 1.4-29.6).

Median follow-up was 42 months (range, 9-115). Overall response rate was 81%; 15 patients (71%) achieved a CR, including

**Table 1. Characteristics of the study population at the start of TMZ treatment and response to TMZ**

Characteristics				Previous treatments						TMZ treatment					
Pt	Age (y)	ISOLD score	CSF tests	Lines of previous treatment	HD MTX	HD cytarabine	ITV MTX	Ritux	ASCT	Other	TMZ duration (mo)	TMZ response	PFS (mo)	OS (mo)	Vital status at last FU/ cause of death
1	53	ND	Cy	2	First line × 3	Second line × 2	N	N	Second line/ C; TCB	N	40	CR	115+	115+	Alive in CR
2	74	9.2	ND	3	N	First line × 2	Third line	Y (second line)	N	Second line: Ritux + idarubicin + ifosfamide	5	CR	73+	73+	Alive in CR
3	81	ND	Cy, Ck	1	N	N	First line	N	N	N	3	CR	52+	52+	Alive in CR
4	85	18.8	ND	0	N	N	N	N	N	N	8	CR	47+	47+	Alive in CR
5	90	9.2	ND	0	N	N	N	N	N	N	6	CR (cerebral and ocular)	40	44	Alive with relapse
6	79	6.7	Cy, Cl, Ck, F <sub>-</sub>	2	First line × 6	N	N	N	N	Second line ibrutinib	25	CR	29+	29+	Alive in CR
7	75	ND	ND	4	First line × 3	Second line × 2	Fourth line	Y (third line)	N	Third line: Ritux + idarubicin + ifosfamide	5	CR	17	18	Death due to cerebral progression
8	72	11.4	Cy	1	First line × 6	First line × 2: dose reduction	N	N	N	N	16	CR	16	30	Alive with relapse
9	87	18.8	ND	2	N	N	First and second line	N	N	N	5	CR	13	26	Death due to cerebral progression
10	73	15	Cy, Cl	2	First line × 6	First line × 2	N	N	2nd line/ C; TCB	Second line: ICE	11	CR	11	14	Death due to cerebral progression
11	80	7.3	Cy, Ck, F	2	First line × 6	First line × 6	N	N	N	Second line: ibrutinib	10	CR	10	11	Alive with relapse
12	67	16	Cy, F	1	First line × 6	First line × 6	N	N	N	N	9+	CR	9+	9+	Alive with CR

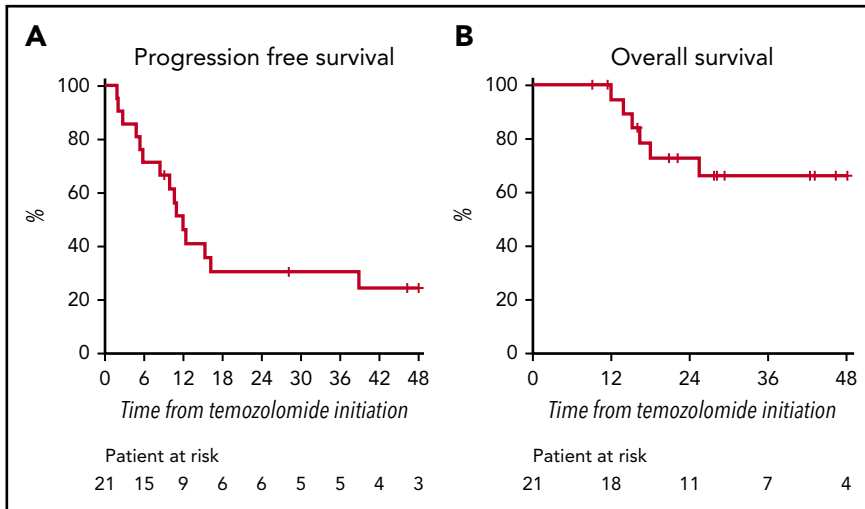
Patient 12 is still receiving treatment with TMZ. Patients 6 and 8 were treated with MTX/ITV for 2 months and lenalidomide for 5 months, respectively. ISOLD score was done in vitreous or AH; a score >4.6 has a 99% probability of LVRP. All patients tested for CSF were negative with all the tests used.  
 C, cerebral; CR, conditioning regimen; Cl, clonality; Ck, cytokine dosage; CR, complete response; Cy, cytology; F, flow cytometry; FU, follow-up; ICE, ifosfamide + carboplatin + etoposide; ITV, intravitreal; N, no; ND, no data; PD, progressive disease; PFS, progression-free survival; PR, partial response; Pt, patient; Ritux, rituximab; Rx, radiotherapy; OS, overall survival; SD, stable disease; TCB, thiotepa + cyclophosphamide + busulfan; Y, yes.

Table 1. (continued)

Characteristics				Previous treatments							TMZ treatment				
Pt	Age (y)	ISOLD score	CSF tests	Lines of previous treatment	HD MTX	HD cytarabine	ITV MTX	Ritux	ASCT	Other	TMZ duration (mo)	TMZ response	PFS (mo)	OS (mo)	Vital status at last FU/ cause of death
13	56	6.6	ND	3	N	First line × 4	Second and third line	N	N	N	8	CR	9	15	Death due to cerebral progression
14	70	ND	ND	1	First line unknown doses	First line unknown doses	N	Y (first line)	N	N	3	CR	6	43	Alive with relapse
15	75	12.9	Cy	2	First line × 6	First line × 2	N	Y (first line)	N	Second line: lenalidomide	5	CR	5	22	Alive with relapse
16	75	ND	Cy	1	First line × 3	First line × 2	N	N	N	First line: cerebral Rx 11 Gy	3	PR	11	81	Alive with relapse
17	44	16	ND	2	First line × 5	First line × 5	N	N	N	Second line: ICE	5	PR	5	28	Alive with relapse
18	74	ND	Cy	1	First line × 6	First line × 2	N	N	N	N	11	PD	11	16	Lost to FU
19	75	9.4	Cy	1	First line × 6	First line × 2	N	N	N	N	5	PD	3	17	Death due to cerebral progression
20	84	ND	ND	1	First line × 6	First line × 2	N	N	N	N	Unknown	PD	2	12	Death due to unknown cause
21	35	ND	Cy	1	First line × 5	N	N	N	N	N	1	PD	2	21	Lost to FU

Patient 12 is still receiving treatment with TMZ. Patients 6 and 8 were treated with MTX/ITV for 2 months and lenalidomide for 5 months, respectively. ISOLD score was done in vitreous or AHT; a score >4.6 has a 99% probability of LVRP. All patients tested for CSF were negative with all the tests used.

C, cerebral; CR, conditioning regimen; CI, clonality; Ck, cytokine dosage; CR, complete response; Cy, cytology; F, flow cytometry; FU, follow-up; ICE, ifosfamide + carboplatin + etoposide; ITV, intravitreal; N, no; ND, no data; PD, progressive disease; PFS, progression-free survival; PR, partial response; Pt, patient; Ritux, rituximab; Rx, radiotherapy; OS, overall survival; SD, stable disease; TCB, thiotepa + cyclophosphamide + busulfan; Y, yes.



**Figure 1. Patient outcomes.** (A) PFS and (B) OS from TMZ initiation.

1 patient with an ocular and cerebral response and 2 patients (10%) with a PR. Four patients had PD. Median duration of response was 10.9 months (range, 3-109 months). At last follow-up, 6 patients are still in CR, including 1 treated in front line, and all but one had stopped TMZ. One patient who had previously received an ASCT is still in CR 115 months after starting treatment. Three patients previously treated with lenalidomide (n = 1) or ibrutinib (n = 2) obtained a CR. Some patients described a visual acuity improvement within a few days. For the patients tested, the course of the IL-10 assays dramatically decreased during the treatment of 9 responder patients and increased for 1 patient who had PD 8 months later.

Median PFS was 12 months (95% CI, 8 not reached) with a 2-year PFS of 30% (95% CI, 15-61) (Figure 1A). Median OS has not yet been reached (Figure 1B). Six patients died, 5 due to cerebral progression.

Three patients had grade 3 toxicities (anemia and vomiting), and 1 patient had 2 grade 4 toxicities (neutropenia and thrombocytopenia). One patient requested discontinuation because a feeling of worsening of memory impairment, but neurological dysfunction had begun before TMZ.

We report here a cohort of patients with PVRL treated with TMZ. The results of molecular and cytokine analyses propose strong arguments for the correct diagnosis and follow-up. First-line IV chemotherapy usually consists of a combination of HD MTX and cytarabine.<sup>10,11</sup> There have been few publications on R/R PVRL and no consensus exists in this field.<sup>12-19</sup> The interest of ASCT in R/R patients has been demonstrated but it concerns only younger patients.<sup>20-22</sup> The efficacy of lenalidomide in PVRL and PCNSL was suggested by Rubenstein et al<sup>12</sup> and was recently confirmed by the LOC network<sup>13,14</sup>. Similarly, ibrutinib has been reported to be effective in the treatment of PVRL and PCNSL.<sup>15,16</sup> However, PFS with these 2 new drugs remains short, toxicity is not negligible, and costs are high.

PFS and OS of patients with isolated PVRL treated in first line are 29.6 and 58 months,<sup>23</sup> and there are no OS data in R/R patients, but the prognosis is usually poor. In our study, patients had usually been treated several times, and some patients had received 4 lines of treatment or ibrutinib, lenalidomide, or ASCT,

thus representing a population with a very poor prognosis and very limited available treatments. All but 1 patient treated for R/R PVRL had received MTX and/or aracytine before, which represents the main drugs for vitreal localization. Few patients received rituximab or local radiation because of lack of proof efficacy.

We report an excellent overall response rate of 81%, a CR of 71%, and long-lasting responses, which represent the best response rates published to date. Median OS was not reached, while median follow-up was 42 months.

No unusual toxicity was observed and, compared with chemotherapy, radiotherapy, lenalidomide, and ibrutinib, TMZ seems to be better tolerated. Comparatively, HD aracytine is associated with 62% grade 3 or 4 myelosuppression.<sup>24</sup>

In economic terms, the very low ratio of cost/benefits of TMZ compared with other drugs used in the same clinical context and until progression, such as ibrutinib or lenalidomide, appears to be very interesting. Limitations include retrospective analysis and lack of central pathologic confirmation.

In summary, TMZ, with its very high overall response rate, low toxicity, and affordable cost, can be considered as a very good therapeutic option and a new reference for elderly patients or R/R PVRL.

## Acknowledgment

The authors acknowledge Network LOC for patients' recruitment and treatments' decisions.

## Authorship

Contribution: M. Baron and S.C. wrote the manuscript; L.B. analyzed statistical data; N.C., C.F., M. Blaizeau, C.S., C.H., K.H.-X., E.G., M.-L.L.L., A.L., P.S., B.B., V.L., V.T., M.-H.E., and D.R.-W. took care of the patients and completed the data forms for the study; C.S., C.H., K.H.-X., P.S., E.G., and S.C. participated in the LOC network and made treatment decisions; and K.M., M.C., and M.L.G.-T. provided biological diagnosis.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: M.B., 0000-0003-0212-8684; E.G., 0000-0002-7651-9189; K.M., 0000-0001-8864-4801; D.R.-W., 0000-0002-7767-755X; M.L.G.-T., 0000-0002-3131-3240.

Correspondence: Marine Baron, Groupe Hospitalo-Universitaire Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France; e-mail: marine.baron@aphp.fr.

## Footnote

For original data, please e-mail the corresponding author.

## REFERENCES

- Chan C-C, Rubenstein JL, Coupland SE, et al. Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. *Oncologist*. 2011;16(11):1589-1599.
- 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(11):901-913.
- Enting RH, Demopoulos A, DeAngelis LM, Abrey LE. Salvage therapy for primary CNS lymphoma with a combination of rituximab and temozolomide. *Neurology*. 2004;63(5):901-903.
- Pitini V, Baldari S, Altavilla G, Arrigo C, Naro C, Perniciaro F. Salvage therapy for primary central nervous system lymphoma with (90)Y-ibritumomab and temozolomide. *J Neurooncol*. 2007;83(3):291-293.
- Reni M, Zaja F, Mason W, et al. Temozolomide as salvage treatment in primary brain lymphomas. *Br J Cancer*. 2007;96(6):864-867.
- Wong ET, Tishler R, Barron L, Wu JK. Immunochemotherapy with rituximab and temozolomide for central nervous system lymphomas. *Cancer*. 2004;101(1):139-145.
- Costopoulos M, Toutou V, Golmard J-L, et al. ISOLD: a new highly sensitive interleukin score for intraocular lymphoma diagnosis. *Ophthalmology*. 2016;123(7):1626-1628.
- van Dongen JJM, van der Velden VHJ, Brüggemann M, Orfao A. Minimal residual disease diagnostics in acute lymphoblastic leukemia: need for sensitive, fast, and standardized technologies. *Blood*. 2015;125(26):3996-4009.
- Abrey LE, Batchelor TT, Ferreri AJ, et al; International Primary CNS Lymphoma Collaborative Group. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. *J Clin Oncol*. 2005;23(22):5034-5043.
- Plotkin SR, Betensky RA, Hochberg FH, et al. Treatment of relapsed central nervous system lymphoma with high-dose methotrexate. *Clin Cancer Res*. 2004;10(17):5643-5646.
- Pentsova E, DeAngelis LM, Omuro A. Methotrexate re-challenge for recurrent primary central nervous system lymphoma. *J Neurooncol*. 2014;117(1):161-165.
- Rubenstein JL, Treseler PA, Stewart PJ. Regression of refractory intraocular large B-cell lymphoma with lenalidomide monotherapy. *J Clin Oncol*. 2011;29(20):e595-e597.
- Houillier C, Choquet S, Toutou V, et al. Lenalidomide monotherapy as salvage treatment for recurrent primary CNS lymphoma. *Neurology*. 2015;84(3):325-326.
- Ghesquieres H, Houillier C, Chinot O, et al. Rituximab-lenalidomide (REVRI) in relapse or refractory primary central nervous system (PCNSL) or vitreo retinal lymphoma (PVRL): results of a "proof of concept" phase II study of the French LOC Network. *Blood*. 2016;128(22):785-785.
- Chamoun K, Choquet S, Boyle E, et al. Ibrutinib monotherapy in relapsed/refractory CNS lymphoma: A retrospective case series. *Neurology*. 2017;88(1):101-102.
- Choquet S, Houillier C, Bijou F, et al. Ibrutinib monotherapy in relapse or refractory primary CNS lymphoma (PCNSL) and primary vitreo-retinal lymphoma (PVRL). Result of the interim analysis of the iLOC phase II study from the Lysa and the French LOC Network. *Blood*. 2016;128(22):784-784.
- 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(4):448-451.
- Ohguro N, Hashida N, Tano Y. Effect of intravitreal rituximab injections in patients with recurrent ocular lesions associated with central nervous system lymphoma. *Arch Ophthalmol*. 2008;126(7):1002-1003.
- Larkin KL, Saboo US, Comer GM, et al. Use of intravitreal rituximab for treatment of vitreoretinal lymphoma. *Br J Ophthalmol*. 2014;98(1):99-103.
- Soussain C, Merle-Béral H, Reux I, et al. A single-center study of 11 patients with intraocular lymphoma treated with conventional chemotherapy followed by high-dose chemotherapy and autologous bone marrow transplantation in 5 cases. *Leuk Lymphoma*. 1996;23(3-4):339-345.
- Soussain C, Hoang-Xuan K, Taillandier L, et al; Société Française de Greffe de Moëlle Osseuse-Thérapie Cellulaire. Intensive chemotherapy followed by hematopoietic stem-cell rescue for refractory and recurrent primary CNS and intraocular lymphoma: Société Française de Greffe de Moëlle Osseuse-Thérapie Cellulaire. *J Clin Oncol*. 2008;26(15):2512-2518.
- Soussain C, Choquet S, Fourme E, et al. Intensive chemotherapy with thiotepea, busulfan and cyclophosphamide and hematopoietic stem cell rescue in relapsed or refractory primary central nervous system lymphoma and intraocular lymphoma: a retrospective study of 79 cases. *Haematologica*. 2012;97(11):1751-1756.
- Grimm SA, Pulido JS, Jahnke K, et al. Primary intraocular lymphoma: an International Primary Central Nervous System Lymphoma Collaborative Group Report. *Ann Oncol*. 2007;18(11):1851-1855.
- Abrey LE, Yahalom J, DeAngelis LM. Treatment for primary CNS lymphoma: the next step. *J Clin Oncol*. 2000;18(17):3144-3150.

DOI 10.1182/blood.2019003073

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