

Efficacy of Procarbazine, Lomustine, and Vincristine Chemotherapy for Recurrent Primary Central Nervous System Lymphomas

Young-Joo Kim¹, Jai-ho Choe², Jae-Hyun Park¹, Yong-Kil Hong¹

¹Department of Neurosurgery, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, Korea

²Department of Neurosurgery, Bundang Jesaeng Hospital, Seongnam, Korea

Received May 18, 2015

Revised June 11, 2015

Accepted July 3, 2015

Correspondence

Yong-Kil Hong
 Department of Neurosurgery,
 Seoul St. Mary's Hospital,
 The Catholic University of Korea
 College of Medicine,
 222 Banpo-daero, Seocho-gu,
 Seoul 06591, Korea
Tel: +82-2-2258-6123
Fax: +82-2-594-4248
E-mail: hongyk@catholic.ac.kr

Background Optimal treatment for recurrent primary central nervous system lymphomas (PCNSLs) has not been defined yet and there is no general consensus about the salvage chemotherapy after high-dose methotrexate (HD-MTX)-based chemotherapy. The purpose of the present study was to evaluate the efficacy and safety of procarbazine, lomustine, and vincristine (PCV) chemotherapy for recurrent PCNSLs.

Methods We reviewed eight immunocompetent patients (five males/three females, mean age: 56 years) who received salvage PCV chemotherapy (procarbazine 60 mg/m², days 8 through 21; CCNU 110 mg/m², day 1; vincristine 2 mg, days 8 and 28) for recurrent PCNSL and two patients switched to PCV chemotherapy due to severe adverse effects of HD-MTX chemotherapy. Radiologic responses, survival, and adverse effects were analyzed.

Results Of the eight recurrent PCNSLs, three patients (37.5%) showed radiologic complete response, one patient (12.5%) showed partial response, and four patients (50%) showed progressive disease after PCV chemotherapy. Median progression free survival (PFS) from the first administration of PCV to relapse or last follow-up was 7 months (range 5–32 months) and median overall survival was 8 months (range 2–41 months). The two patients who switched to PCV chemotherapy showed PFS of 9 and 5 months from the beginning of PCV to relapse. The common side effects were thrombocytopenia, neutropenia, and peripheral neuropathy. There were 4 grade III or IV myelo-suppression, but no fatal complications, including severe hemorrhage or infection, were observed.

Conclusion Salvage PCV chemotherapy has a moderate anti-lymphoma activity for recurrent PCNSLs after the HD-MTX-based chemotherapy with tolerable toxicity.

Key Words Lymphoma; Central nervous system; Salvage therapy; Chemotherapy; Methotrexate.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare malignant brain tumor that accounts for about 3% of newly-diagnosed primary brain tumors. PCNSL can affect variable parts of the CNS, including brain, spinal cord, leptomeninges, and eyes without evidence of systemic involvement. Even though PCNSL is a variant of extranodal non-Hodgkin's

lymphoma, the regimen traditionally used in systemic lymphoma chemotherapy is usually ineffective in PCNSL because of the blood-brain barrier [1]. If untreated, patients usually survive for only a few months. However, since the introduction of high dose methotrexate (HD-MTX)-based regimen, prognosis of newly-diagnosed PCNSL has significantly improved to more than 50% complete response (CR) rate and 22 to 55.8 months median overall survivals (OS) [2-6].

Although durable remission can be achieved by using HD-MTX-based regimen for several years, most PCNSL patients suffer tumor progression or relapse [7,8]. The prognosis of relapsed or refractory PCNSL is poor with the median OS of about 4.5 months [9]. Therefore, salvage treatment is needed

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © 2015 The Korean Brain Tumor Society, The Korean Society for Neuro-Oncology, and The Korean Society for Pediatric Neuro-Oncology

in patients who show tumor relapse and disease progression. However, general consensus or guidelines for relapsed or refractory PCNSLs have not been established yet and limited therapeutic options are available after the relapse of PCNSLs compared to newly-diagnosed tumor. Retreatment with HD-MTX; surgical resection; temozolomide; topotecan; etoposide, ifosfamide and cytarabine; procarbazine, lomustine (CCNU), and vincristine (PCV); high-dose chemotherapy followed by autologous stem cell transplantation; rituximab with or without temozolomide; pemetrexed; bendamustine; radiotherapy have all been introduced with varying results [7,8,10-24]. The aim of this study is to evaluate the efficacy and safety of PCV chemotherapy as a salvage therapy for refractory or relapsed PCNSLs after HD-MTX-based regimen.

MATERIALS AND METHODS

Patient selection

From October 1998 to November 2012, 23 newly-diagnosed PCNSLs were treated using HD-MTX monotherapy as the first-line therapy. Among these patients, salvage PCV chemotherapy was adopted for eight refractory or relapsed PCNSL patients and two patients who ceased HD-MTX due to side effects. The patient characteristics included: age ≥ 18 , failed initial HD-MTX therapy and/or radiotherapy, Karnofsky performance scale (KPS) ≥ 60 , histologically confirmed PCNSL, negative human immunodeficiency virus serology and adequate laboratory examinations (absolute neutrophil count $\geq 1,500/\text{mm}^3$, hemoglobin ≥ 8.0 g/dL, platelet counts $\geq 100,000/\text{mm}^3$, creatinine clearance > 50 mL/min, and sGOT/sGPT ≤ 2 times upper limit of normal). Thirteen patients did not receive PCV chemotherapy for the following reasons. Four patients maintained complete remission after the initial HD-MTX monotherapy. One patient who experienced acute renal failure had to stop HD-MTX chemotherapy and switched to WBRT because of elevated serum creatinine level. Six patients received intravenous steroid injection followed by WBRT as salvage therapy due to their general conditions, including decreased mentality and swallowing difficulty. Of the six patients treated with WBRT and steroid, four patients died due to disease progression and two patients recovered without recurrence. Remained two patients refused additional salvage treatment after tumor relapse and received conservative care. Medical records and radiologic examinations were retrospectively reviewed for ten patients who received salvage PCV chemotherapy. The review of patient medical records and radiologic examinations was approved by the Institutional Review Board of Seoul St. Mary's Hospital (approval number: KC13RISI0232).

Treatment protocol

Treatment strategy for recurrent or relapsed PCNSLs in our hospital is demonstrated in Fig. 1. The patients who showed CR after the first-line HD-MTX therapy and completed nine cycles were treated with re-challenging of HD-MTX monotherapy (reMTX) as the the second-line treatment. PCV chemotherapy was considered as the main second-line regimen for PCNSLs that were refractory to HD-MTX or reMTX and re-relapsed after reMTX chemotherapy. Whenever possible, we avoided WBRT because of its neurotoxicity; it was only applied to the patients who were not able to maintain chemotherapy due to their poor general condition.

All ten patients received HD-MTX monotherapy after histologic confirmation as the first-line treatment. PCV chemotherapy was the second-line treatment for six patients, the third-line treatment for three patients, and the fourth-line therapy for one patient. Two patients received the third-line PCV chemotherapy after the initial HD-MTX and the second-line reMTX therapy. One patient who decreased KPS to 50 because of disease progression and related brain swelling during HD-MTX monotherapy received radiotherapy combined with steroid as the second-line treatment and subsequently received PCV chemotherapy as the third-line therapy after a second relapse (patient 6). The patient who received the fourth-line PCV chemotherapy was refractory to reMTX with disease progression and experienced a second relapse after radiotherapy combined with steroid (patient 5). No patients received adjuvant steroid therapy during PCV chemotherapy (Table 1).

HD-MTX chemotherapy (8 g/m^2 for three cycles as the induction phase and 3.5 g/m^2 for six cycles as the maintenance phase) protocol and radiation dose ($5,040\text{--}5,440$ cGy) were the same as in our previous publication [4]. We administered

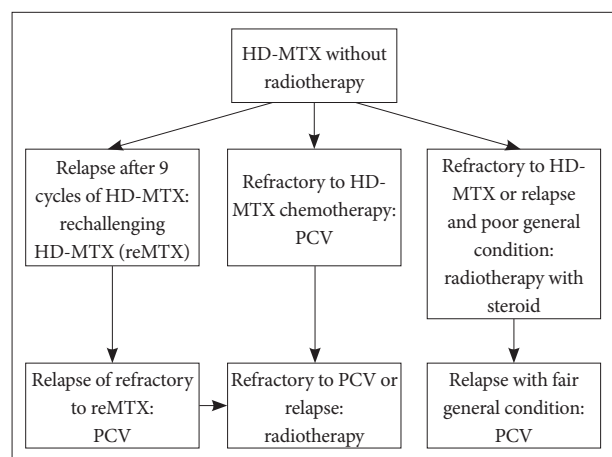


Fig. 1. Treatment strategy for recurrent or relapsed PCNSLs. HD-MTX, high dose methotrexate; PCNSLs, primary central nervous system lymphomas; PCV, procarbazine, lomustine, and vincristine; reMTX, re-challenging of HD-MTX monotherapy.

Table 1. Characteristics and treatments of PCNSL patients

Case	Age	Sex	KPS before PCV	1st line therapy (response/duration*)	2nd line therapy (response/duration*)	3rd line therapy (response/duration*)	4th line therapy (response/duration*)	Cycles of PCV	PFS	OS
1	59	M	100	HD-MTX (PD)	PCV (CR/32)	RT (CR/9)	-	7	32	41+
2	54	M	90	HD-MTX (CR/25)	reMTX (CR/11)	PCV (CR/5)	RT (CR/8)	3	5	14
3	71	M	70	HD-MTX (PD)	PCV (PD)	RT (CR/4)	-	1	0	7
4	66	F	70	HD-MTX (CR/7)	PCV (PD)	RT (PR/1)	-	1	0	2
5	72	M	60	HD-MTX (CR/71)	reMTX (PD)	RT (CR/14)	PCV (PD)	2	0	5
6	63	F	90	HD-MTX (PD)	RT (CR/7)	PCV (CR/13)	-	5	13+	13+
7	36	F	80	HD-MTX (PR/5)	PCV (PD)	RT (PR/5)	-	1	0	8
8	39	M	100	HD-MTX (PD)	PCV (PR/7)	RT (CR/4)	-	4	7	11+
9	47	F	90	HD-MTX (ARF [†] /12)	PCV (CR/9)	RT (CR/8)	-	4	9	18+
10	52	F	100	HD-MTX (CR/41)	reMTX (ARF [†] /9)	PCV (CR/5)	RT (CR/7)	3	5	12+

*duration: months, †ARF: ceased due to acute renal failure. CR, complete response; HD-MTX, high dose methotrexate; OS, overall survival; PCNSL, primary central nervous system lymphoma; PCV, procarbazine, lomustine, and vincristine; PFS, progression free survival; reMTX, re-challenging of HD-MTX monotherapy; RT, radiotherapy

the PCV chemotherapy following the same protocol used in malignant glioma (procarbazine 60 mg/m², days 8 through 21; CCNU 110 mg/m², day 1; vincristine 2 mg, days 8 and 28). Foods containing tyramine were restricted when administering procarbazine. The patients underwent laboratory and clinical evaluations for toxicity twice a month (day 8 and 28 of every cycle). Each course of PCV chemotherapy was delayed until the patients recovered if Common Terminology Criteria for Adverse Events (CTCAE ver 4.0) criteria of grade III or IV toxicity were evident. Vincristine dose was reduced by 20% to 1.6 mg for the patients who suffered peripheral neuropathy. A 4-week break between each chemotherapy cycle was needed and PCV chemotherapy was continued until disease progression or recurrence.

Assessment of response and toxicity

Clinical data including neurologic and laboratory examinations were assessed at baseline and then twice (day 8 and 28) per each cycle of PCV chemotherapy. The response to PCV chemotherapy was evaluated by International Primary CNS Lymphoma Collaboration Group guideline [25] before the start of 2nd, 4th, and 6th cycle. Cerebrospinal fluid (CSF)-positivity and vitreoretinal involvement were examined at baseline, termination of treatment, and whenever needed to evaluate by spinal tap and consultation to ophthalmology. When neurologic symptoms developed or KPS score decreased by more than 20 during PCV chemotherapy, brain imaging was immediately performed and the decision whether to commence another treatment or not was made. Acute toxicity was graded according to the CTCAE toxicity criteria.

Statistical analyses

OS and progression free survival (PFS) were estimated by

the Kaplan-Meier method. Comparisons of survival curves were made by the log-rank test and the null hypothesis of no difference was rejected if *p*-values were below 0.05.

PFS was calculated from the date of the first administration of PCV chemotherapy to the date of relapse or the last follow-up. OS was measured from date of the first administration to death or the last follow-up. Mann-Whitney U test was used to analyze continuous variables, χ^2 or Fisher's exact test was used for categorical variables. Kaplan-Meier and log-rank method was used for the estimation of OS and PFS. All analyses were performed using SPSS software (version 18, SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Five of ten patients were male. Mean age at the initial diagnosis was 56.5 years (range: 36–72 years) and KPS before PCV chemotherapy ranged from 60 to 100 (median: 90). Median number of PCV chemotherapy cycles was 3 (range: 1–7) and the median follow-up period was 27 months (range: 10–105 months). To confirm the initial pathology, we performed three navigation-guided stereotactic biopsies, two endoscopic biopsies for intra-ventricular lesions, and five craniotomies. All patients were diagnosed with diffuse large B-cell lymphoma. One patient had CSF involvement at initial diagnosis (patient 1). There was one patient with initial ocular involvement (patient 6) and an additional ocular lymphoma developed in four patients during treatment.

Response and survival

Objective response rate was 50% (four of eight relapse or refractory PCNSL patients). Three of them were complete re-

missions (CRs) and one was partial remission (PR). No complete remission, unconfirmed was noted. Four patients showed disease progression despite PCV chemotherapy (Table 1).

PFS of the four patients with response to PCV chemotherapy was 32, 5, 13+, and 7 months, respectively, and median PFS was 7 months. Radiotherapy for three re-relapse patients after PCV chemotherapy was done and all of them achieved CR after radiotherapy. Two patients remained alive without relapse, while the others experienced relapse and died. Median OS in the PCV response group was 14 months. In the non-response group, three patients underwent radiotherapy after disease progression. One patient who underwent radiotherapy prior to PCV chemotherapy refused additional treatment and expired 3 months afterwards under hospice care (patient 5). CR after radiotherapy was achieved temporarily in one patient, but relapse was developed 4 months later (patient 3). Two patients showed PRs to radiotherapy, but eventually died due to disease progression. OS from the first administration of PCV chemotherapy to death was 7, 2, 5, and 8 months. Median OS was 5 months and cumulative OS was lower in the non-response group compared to the response group ($p=0.007$) (Fig. 2). Median OS of all patients was 8 months.

Two patients (patients 9 and 10) were switched to PCV chemotherapy because of acute renal failure during HD-MTX chemotherapy. CR was maintained for 5 months in one and for 9 months in the other patient. Both patients underwent radiotherapy after re-relapse and remained alive with maintaining CR state.

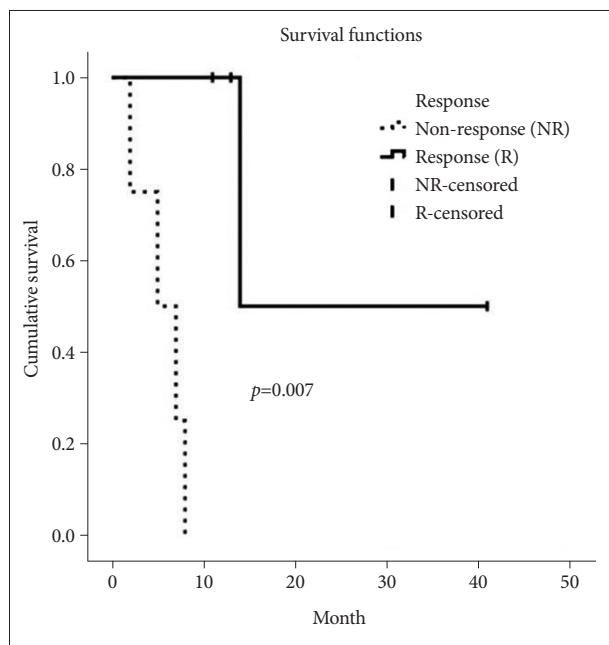


Fig. 2. Cumulative overall survival according to response to PCV chemotherapy. PCV, procarbazine, lomustine, and vincristine.

Toxicity

A total of 31 cycles of PCV chemotherapy were performed. Common side effects included thrombocytopenia, neutropenia, and peripheral neuropathy. Due to NCI toxicity grade III or IV thrombocytopenia and neutropenia, we had to postpone PCV chemotherapy in four patients (Table 2). With platelet transfusion and G-CSF administration, no fatal complications, such as massive gastrointestinal bleeding, cerebral hemorrhage, or severe infection, occurred. There were four patients with grade I peripheral neuropathy. However, after vincristine dose modification, the symptom improved. There was no reported toxic hepatitis and allergic dermatitis. The neurotoxicity including cognitive dysfunction and leukoencephalopathy did not occur during PCV chemotherapy. Median KPS after last cycle of PCV chemotherapy was 90 (range 50 to 100) which was similar to median KPS before the therapy. The two patients in the non-response group decreased KPS score because of disease progression.

DISCUSSION

PFS and OS of newly-diagnosed PCNSL patients have increased with the development of aggressive multimodality treatments; however, but most patients still require salvage therapy due to disease progression or relapse. There was no general consensus or established optimal treatment for relapsed or progressive PCNSLs. Several regimens, including single or multiple combinations of chemotherapy with or without radiation as a salvage treatment, have been reported in small single center series with variable OS ranging from 3.5 to 16 months (Table 3) [10-17,26]. Temozolomide with or without rituximab has been used as salvage therapy in several reports with OS ranging from 3.5 to 14 months [11,15,17,26]. While temozoloimde has replaced PCV chemotherapy in many indications, we opted for PCV chemotherapy, as using temozolomide for PCNSL is considerably more expensive than PCV chemotherapy in our country. Nevertheless, several reports showed that the effect of temozolomide for PCNSLs was not superior as compared to PCV chemotherapy [11,15,17,18,26]. Although those trials are not controlled studies, we considered cost-effectiveness of temozolomide and decided to use PCV chemotherapy for recurrent PCNSLs. The PFS of 7 months and OS of 8 months in our study are

Table 2. Toxicity according to National Cancer Institute toxicity criteria

	Grade I	Grade II	Grade III	Grade IV
Neutropenia	1		2	2
Thrombocytopenia	1	1	4	
Peripheral neuropathy	4			
Anorexia		1		

Table 3. Trials on salvage treatment for refractory and relapse PCNSL

Reference	Nature of study	Treatment modality	Patient number	Objective response rate (%)	Progression free survival (mo)	Overall survival (mo)
Herrlinger, 2000	Retrospective	PCV	7	86	NA	16+
Soussain, 2001	Retrospective	IC+HCR	22	72.7	53% at 36 mo	63.7% at 36 mo
Arellano-Rodrigues, 2003	Retrospective	VIA	16	37	5	41% at 12 mo
Wong, 2004	Retrospective	TMZ with retuximab	7	100	6	8
Enting, 2004	Retrospective	TMZ with retuximab	15	53	7.7	14
Plotkin, 2004	Retrospective	HD-MTX	22	91	25.8	61.9
Reni, 2004	Prospective	TMZ	23	26	6+	3.5+
Nguyen, 2005	Retrospective	WBRT	27	74	9.7	10.9
Fischer, 2006	Prospective	Topotecan	27	33	2	8.4
Hottinger, 2007	Retrospective	WBRT	48	79	10	16
Makino, 2012	Retrospective	TMZ	17	58	1.9	6.7
Chamberlain, 2014	Retrospective	Bendamusine	12	58	3.5	5.5
This study	Retrospective	PCV	8	57	7	8+

HD-MTX, high dose methotrexate; IC+HCR, intensive chemotherapy with hematopoietic stem-cell rescue; NA, not available; PCNSL, primary central nervous system lymphoma; PCV, procarbazine, lomustine, and vincristine; TMZ, temozolomide; VIA, etoposide (VP-16), ifosfamide, cytarabine (Ara-C); WBRT, whole brain radiotherapy

comparable to the results of temozolomide treatment. Plotkin et al. [19] reported excellent results with 91% response rate and 61.9 months OS after retreatment with HD-MTX for relapsed PCNSLs. A limitation of this study is that the enrolled group was limited to the patients who achieved a CR with the initial HD-MTX based chemotherapy. Salvage WBRT also showed a good treatment outcome with 74–79% radiologic response and 10.9–16 months OS. However, 15 to 29% of the patients developed delayed neurotoxicity, which significantly contributed to the reduced quality of life after radiotherapy [13,14]. Recurrent or refractory PCNSLs treated with high-dose chemotherapy followed by autologous stem cell transplantation by Soussain et al. [16] reported a response rate of 81% and a 1-year survival of >75%, but substantial grade IV neutropenia and thrombocytopenia developed in all patients and two of 22 patients (9%) died due to toxicity.

We adopted PCV chemotherapy as salvage treatment for several reasons. First, PCV chemotherapy has shown efficacy as the first-line adjuvant therapy after radiotherapy with hydroxyurea [27] and as the second-line therapy for recurrent PCNSL [18]. Second, the action mechanism of PCV chemotherapy as alkylation is different from methotrexate as anti-metabolites. Third, CCNU and procarbazine can penetrate the blood-brain barrier. Finally, PCV chemotherapy is familiar to clinicians because it has been traditionally used for other brain tumors with tolerable toxicity profiles. Table 1 summarizes the complex treatment histories of the patients. While our data present diverse treatment modalities and results, there are several common points, even though the number of the patients was small. These are as follows: 1) Cases refracto-

ry to PCV chemotherapy did not respond well to radiotherapy (CR: one patient, PR: two patients); 2) The PCV non-response group had a lower pretreatment mean KPS score as compared to the PCV response group ($p=0.009$); 3) Patients with a low KPS score (<80) showed a lower OS compared to the patients showing a high KPS score (≥ 80) ($p=0.017$); 4) In the elderly group (over 60 years old), median OS of 5 months was lower than in the younger group with 14 months OS. While this is a trend ($p=0.101$), statistical significance was not established due to small sample size; 5) Refractory or relapsed PCNSLs are sensitive to salvage radiotherapy with 80% (8 of 10 patients) CR and 20% PR rate, similarly to the previous report. These data support that the most important prognostic factors can be age and performance status in recurrent disease, as well as in newly-diagnosed PCNSLs [28]. It should also be emphasized that, since three patients received only one cycle (4 people within 2 cycles, 6 people within 3 cycles) at earlier stages, the patient selection is also an important factor. There was one preliminary report of salvage PCV chemotherapy for seven relapsed or refractory PCNSL patients with 86% response rate (CR: 57%, PR: 28%) and 16+ months OS [18]. In this report, the authors suggested that there might be an overestimation of the response rate because of additional corticosteroid medication in two patients. Glucocorticoid medication was both a therapeutic agent against lymphoma cells and might have significantly affected imaging characteristics of these lesions. Consequently, patients' clinical and radiologic improvements could be achieved with steroid therapy and the effect of chemotherapy might be obscure if it is combined with steroid therapy. Since we did not use gluco-

corticoid medication combined with PCV chemotherapy, the reported effects of PCV chemotherapy represent a true anti-lymphoma activity in our study.

The most serious complication of PCV chemotherapy in our study was myelosuppression. There were four patients who postponed PCV chemotherapy due to grade III or IV neutropenia and thrombocytopenia. Peripheral neuropathy was the second common side effect and led to 20% dose reduction of vincristine in four patients. No fatal complication developed during total PCV cycles. PCV chemotherapy has a moderate toxicity, but it can be sufficiently managed.

The limitations of the present study include a small patient number, retrospective nature, heterogeneous treatment regimen before PCV chemotherapy and the lack of molecular study. In addition, it was unclear which drug was effective in the patients who switched PCV due to HD-MTX side effects. Despite these limitations, our data support the effectiveness of PCV chemotherapy for a subset of recurrent PCNSL. Also, salvage PCV chemotherapy can provide a chance to achieve a durable remission without radiotherapy, with the possibility of delaying radiation and retaining radiotherapy as another salvage therapy.

In conclusion, the outcome of this study shows that salvage PCV chemotherapy has a moderate anti-lymphoma activity for recurrent or refractory PCNSLs after the HD-MTX based regimen with tolerable toxicity.

Conflicts of Interest

The authors have no financial conflicts of interest.

REFERENCES

- Schultz C, Scott C, Sherman W, et al. Preirradiation chemotherapy with cyclophosphamide, doxorubicin, vincristine, and dexamethasone for primary CNS lymphomas: initial report of radiation therapy oncology group protocol 88-06. *J Clin Oncol* 1996;14:556-64.
- Gerstner ER, Carson KA, Grossman SA, Batchelor TT. Long-term outcome in PCNSL patients treated with high-dose methotrexate and deferred radiation. *Neurology* 2008;70:401-2.
- Pels H, Schmidt-Wolf IG, Glasmacher A, et al. Primary central nervous system lymphoma: results of a pilot and phase II study of systemic and intraventricular chemotherapy with deferred radiotherapy. *J Clin Oncol* 2003;21:4489-95.
- Yang SH, Lee KS, Kim IS, et al. Long-term survival in primary CNS lymphoma treated by high-dose methotrexate monochemotherapy: role of STAT6 activation as prognostic determinant. *J Neurooncol* 2009;92:65-71.
- Batchelor T, Carson K, O'Neill A, et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. *J Clin Oncol* 2003;21:1044-9.
- Thiel E, Korfel A, Martus P, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. *Lancet Oncol* 2010;11:1036-47.
- Reni M, Ferreri AJ. Therapeutic management of refractory or relapsed primary central nervous system lymphomas. *Ann Hematol* 2001;80 Suppl 3:B113-7.
- Reni M, Ferreri AJ, Villa E. Second-line treatment for primary central nervous system lymphoma. *Br J Cancer* 1999;79:530-4.
- Jahnke K, Thiel E, Martus P, et al. Relapse of primary central nervous system lymphoma: clinical features, outcome and prognostic factors. *J Neurooncol* 2006;80:159-65.
- Arellano-Rodrigo E, López-Guillermo A, Bessell EM, Nomdedeu B, Montserrat E, Graus F. Salvage treatment with etoposide (VP-16), ifosfamide and cytarabine (Ara-C) for patients with recurrent primary central nervous system lymphoma. *Eur J Haematol* 2003;70:219-24.
- Enting RH, Demopoulos A, DeAngelis LM, Abrey LE. Salvage therapy for primary CNS lymphoma with a combination of rituximab and temozolomide. *Neurology* 2004;63:901-3.
- Fischer L, Thiel E, Klasen HA, et al. Prospective trial on topotecan salvage therapy in primary CNS lymphoma. *Ann Oncol* 2006;17:1141-5.
- Hottinger AF, DeAngelis LM, Yahalom J, Abrey LE. Salvage whole brain radiotherapy for recurrent or refractory primary CNS lymphoma. *Neurology* 2007;69:1178-82.
- Nguyen PL, Chakravarti A, Finkelstein DM, Hochberg FH, Batchelor TT, Loeffler JS. Results of whole-brain radiation as salvage of methotrexate failure for immunocompetent patients with primary CNS lymphoma. *J Clin Oncol* 2005;23:1507-13.
- Reni M, Mason W, Zaja F, et al. Salvage chemotherapy with temozolomide in primary CNS lymphomas: preliminary results of a phase II trial. *Eur J Cancer* 2004;40:1682-8.
- Soussain C, Suzan F, Hoang-Xuan K, et al. Results of intensive chemotherapy followed by hematopoietic stem-cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma. *J Clin Oncol* 2001;19:742-9.
- Wong ET, Tishler R, Barron L, Wu JK. Immunochemotherapy with rituximab and temozolomide for central nervous system lymphomas. *Cancer* 2004;101:139-45.
- Herrlinger U, Brugger W, Bamberg M, Küker W, Dichgans J, Weller M. PCV salvage chemotherapy for recurrent primary CNS lymphoma. *Neurology* 2000;54:1707-8.
- Plotkin SR, Betensky RA, Hochberg FH, et al. Treatment of relapsed central nervous system lymphoma with high-dose methotrexate. *Clin Cancer Res* 2004;10:5643-6.
- Shaw EG, Berkey B, Coons SW, et al. Recurrence following neurosurgery-determined gross-total resection of adult supratentorial low-grade glioma: results of a prospective clinical trial. *J Neurosurg* 2008;109:835-41.
- DeAngelis LM, Kreis W, Chan K, Dantis E, Akerman S. Pharmacokinetics of ara-C and ara-U in plasma and CSF after high-dose administration of cytosine arabinoside. *Cancer Chemother Pharmacol* 1992;29:173-7.
- McLaughlin P, Velasquez WS, Redman JR, et al. Chemotherapy with dexamethasone, high-dose cytarabine, and cisplatin for parenchymal brain lymphoma. *J Natl Cancer Inst* 1988;80:1408-12.
- Raizer JJ, Rademaker A, Evens AM, et al. Pemetrexed in the treatment of relapsed/refractory primary central nervous system lymphoma. *Cancer* 2012;118:3743-8.
- Chamberlain MC. Salvage therapy with bendamustine for methotrexate refractory recurrent primary CNS lymphoma: a retrospective case series. *J Neurooncol* 2014;118:155-62.
- Abrey LE, Batchelor TT, Ferreri AJ, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. *J Clin Oncol* 2005;23:5034-43.
- Makino K, Nakamura H, Hide T, Kuratsu J. Salvage treatment with temozolomide in refractory or relapsed primary central nervous system lymphoma and assessment of the MGMT status. *J Neurooncol* 2012;106:155-60.
- Chamberlain MC, Levin VA. Primary central nervous system lymphoma: a role for adjuvant chemotherapy. *J Neurooncol* 1992;14:271-5.
- Ferreri AJ, Blay JY, Reni M, et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. *J Clin Oncol* 2003;21:266-72.