

# Primary CNS lymphoma in the elderly: temozolomide therapy and MGMT status

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**Abstract** This retrospective series explores temozolomide monotherapy in elderly patients with primary CNS lymphoma (PCNSL) and severe comorbidities. In 17 patients (62–90 years old), the complete response rate was 47%, median progression-free survival was 5 months, and median overall survival was 21 months. Five of 17 patients (29.4%) had prolonged responses for at least 12 months and survived for more than 24 months. Three of these patients had a methylated O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) promoter, while the MGMT status was not assessable in the remaining two patients.

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Temozolomide monotherapy appears to be effective in a subgroup of elderly PCNSL patients and deserves further evaluation.

**Keywords** Primary central nervous system lymphoma · Chemotherapy · Temozolomide · MGMT

## Introduction

High-dose methotrexate (HD-MTX)-based chemotherapy is the standard therapy for patients with primary CNS lymphoma (PCNSL). This treatment can also be applied to elderly patients without substantial toxicity as long as organ functions, especially renal function, are adequate [1]. Some elderly patients, however, cannot receive HD-MTX because of more markedly impaired renal function (creatinin clearance < 50 ml/min) or other comorbidities. No standard of care has been defined for this group of patients. Whole brain radiotherapy (WBRT) may not be appropriate because of the increased risk of late neurotoxicity in the elderly and its overall limited efficacy with a median survival time of 12 months [2]. This warrants the search for new chemotherapy regimens for these patients. The alkylating agent temozolomide (TMZ) penetrates into the brain well and has shown some efficacy in the second-line therapy of PCNSL [3–5]; furthermore, it is likely to be tolerated better than HD-MTX in patients with comorbidities. Thus, TMZ may be a promising treatment for elderly patients with PCNSL who cannot receive HD-MTX. As O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation is highly predictive for survival in TMZ-treated glioblastoma patients [6], we also determined the MGMT promoter methylation status in the majority of our patients.

## Patients and methods

We reviewed the charts of four German medical centers to identify PCNSL patients treated with primary TMZ chemotherapy, and analyzed toxicity, response to therapy and survival parameters in these patients. The best response to therapy was assessed in the absence of steroids by contrast-enhanced MRI according to the criteria established by Macdonald et al. [7]. Toxicity was graded according to the World Health Organization classification.

For the analysis of the MGMT promoter methylation status, genomic DNA was extracted from formalin-fixed paraffin-embedded tumor samples and subjected to bisulfite conversion using the EZ DNA Methylation-Gold Kit<sup>TM</sup> (HIS Diagnostics, Freiburg, Germany) or the EpiTect Bisulfite Kit (Qiagen, Hilden, Germany). Bisulfite converted DNA was then analyzed by the authors using methylation-specific PCR (MSP) [8] or direct pyrosequencing [9] in all patients with a sufficient amount of paraffin-embedded tumor tissue available (for detailed descriptions of the methylation assays, see [8, 9]).

## Results

Seventeen patients with histologically proven PCNSL and a median age of 75 years (range 62–90 years; Table 1) who received first-line therapy with TMZ (100–200 mg/m<sup>2</sup> on days 1–5 of a 28-day cycle) were identified. Two of the 17 patients have been previously reported [10]. HD-MTX therapy was regarded inappropriate because of impaired renal function (patients 3, 4, 6, 12 of Table 1), high age (patients 5, 7, 9, 11, 13–17), problems with fluid and electrolyte balance due to a syndrome of inadequate anti-diuretic hormone secretion (SIADH; patient 1), extensive edema (patient 2), severe cardiovascular disease (patient 10), or non-compliance due to oligophrenia (patient 8). The median number of TMZ cycles applied was three (range 1–8 cycles).

Two patients (12%) developed WHO high-grade hematotoxicity: patient 3 had grade 4 leukopenia and thrombocytopenia with subsequent severe infection; patient 4 had grade 4 leukopenia and grade 3 thrombocytopenia. One patient (no. 8) developed grade 1 skin erythema, which might possibly be associated with TMZ therapy. One patient (no. 15) had to discontinue treatment due to

**Table 1** Patient characteristics, treatment outcome and MGMT promoter methylation status of patients with primary central nervous system lymphoma treated with first-line temozolomide (TMZ)

Patient no.	Age at diagnosis (years), gender	Dose (mg/m <sup>2</sup> /d), No. of TMZ cycles <sup>a</sup>	Response to TMZ <sup>b</sup>	PFS (months)	Further therapy at relapse (response)	OS (months)	MGMT status
1	63, m	200, 8 cycles	CR	72+	Still in CR	72+	+
2	75, f	200, 4 cycles	CR	5	7 × TMZ (PR) and WBRT (CR)	21	NA
3	78, f	200, 1 cycle	CR	21	1 × PCV (NA), WBRT (CR)	33	NA
4	72, f	150, 3 cycles	PR	5	WBRT (CR)	21	+
5	72, f	200, 3 cycles	PD	3	WBRT (NA)	8	–
6	77, f	200, 1 cycle	PD	1	None	1	NA
7	90, f	100, 3 cycles	CR	5	None	7	NA
8	62, m	200, 1 cycle	CR	5	3 × TMZ (PD), PCV (NA)	9	–
9	88, f	100, 4 cycles	PD	4	Rituximab (NA)	5+	NA
10	73, m	200, 2 cycles	CR	24+	Still in CR	24+	+
11	82, f	150, 1 cycle	PD	1	None	2	+
12	67, f	200, 2 cycles	PD	3	WBRT (CR)	16+	–
13	81, m	150, 1 cycle	PD	1	None	1	–
14	75, f	150, 1 cycle	PD	1	None	2	+
15	74, m	150, 1 cycle	CR	26+	Still in CR	26+	NA
16	85, m	150, 3 cycles	PD	2	None	3	NA
17	80, f	200, 8 cycles	CR	29+	Still in CR	29+	+

m male, f female, NA not assessable, PFS progression-free survival, OS overall survival, CR complete response, PR partial response, PD progressive disease, TMZ temozolomide; PCV procarbazine, CCNU vincristine, WBRT whole brain radiotherapy (39.6–45 Gy), MGMT O<sup>6</sup>-methylguanine-DNA methyltransferase, + methylated MGMT promoter; – non-methylated MGMT promoter

<sup>a</sup> All patients received standard TMZ treatment (days 1 to 5 out of a 28-day cycle)

<sup>b</sup> All patients were off steroids at the time of response evaluation

spondylodiscitis, and another patient (no. 5) had grade 2 colitis with an unclear causal association to TMZ therapy.

Eight patients (47%) had a complete response (CR), one patient had a partial response (PR), and another eight patients had progressive disease (PD) (Table 1). The median progression-free survival (mPFS) was 5 months (range 1–72+ months; Fig. 1a). Five of 17 patients (29.4%) had prolonged responses for more than 12 months. The median overall survival (mOS) was 21 months (range 1–72+ months; Fig. 1b). The estimated 2-year survival rate was 39.7%. Second- and third-line therapies are listed in Table 1. In four patients (patients 2, 4, 5, and 12), progression-free survival (PFS) after second-line WBRT was longer than PFS after primary TMZ chemotherapy.

Tumor specimens of ten patients were available for MGMT analysis. MGMT promoter methylation (mMGMT; Table 1) in the tumor tissue was found in six patients, while four patients had a non-methylated MGMT promoter (nmMGMT). Overall survival was 21+ months in the group of mMGMT patients, whereas mOS was 9 months in

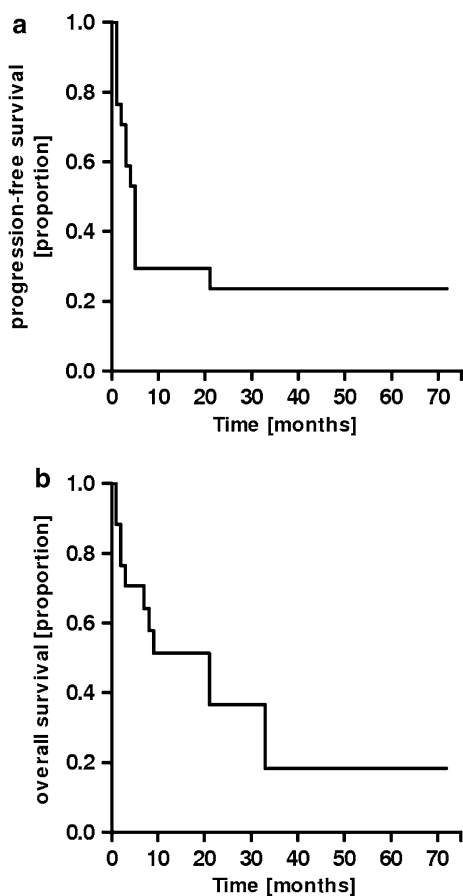
the group of nmMGMT patients. Furthermore, mPFS was 5+ months in mMGMT patients and 3 months in nmMGMT patients. Of note, three of the five patients surviving for 24 months or more had a methylated MGMT promoter, while MGMT was not assessable in two of these patients.

## Discussion

First-line chemotherapy with TMZ shows good tolerability and some activity in elderly PCNSL patients. CR rate (47%), mPFS (5 months) and mOS (21 months) compare well to presumably more toxic regimens such as chemotherapy on a HD-MTX, lomustine and procarbazine base (CR rate 42–47%, mPFS 5.9–6.8 months and mOS 14.3–15.4 months) [11, 12]. Survival with TMZ monotherapy is somewhat shorter than with a combination of HD-MTX and TMZ (CR 55%, mPFS 8 months, mOS 35 months) [13]. However, it is possible that selection bias negatively impacted survival data in our study because many older patients with severe comorbidities participated in the study.

Similar to what has been shown for the combination of HD-MTX/lomustine/procarbazine [12], our patient population falls into two subgroups: (1) the larger group of patients not responding at all to chemotherapy or rapidly progressing after a very short period of response and (2) the smaller group of patients deriving notable benefit from chemotherapy with extended PFS and a high potential for long-term survival (4 of 17 patients surviving relapse-free for substantially more than 2 years). Our MGMT promoter methylation data are compatible with the notion that sustained response and prolonged survival are not possible in the presence of a non-methylated MGMT promoter (PFS 1–3 months). Since none of the patients surviving more than 24 months had a non-methylated MGMT promoter, it may be speculated that a methylated MGMT promoter is a necessary prerequisite for a sustained response. However, a methylated MGMT promoter cannot be the only molecular factor influencing response and survival since three of our patients with a methylated MGMT promoter nevertheless had a short PFS of less than 5 months. Certainly, our limited MGMT data do not sufficiently substantiate this hypothesis, which has to be further explored in trials that apply alkylating agents to patients with PCNSL. Only larger trials will then allow statistical comparison of survival parameters between mMGMT and nmMGMT patients. Of note, salvage WBRT was an effective therapy in four of five patients.

The treatment of elderly patients with PCNSL remains a challenge. According to our preliminary data, TMZ therapy may be an option for some of these patients. The efficacy



**Fig. 1** Kaplan–Meier estimates are shown for **a** progression-free survival (median, 5 months) and **b** overall survival (median, 21 months) in 17 elderly patients with primary central nervous system lymphoma treated with first-line TMZ chemotherapy

of TMZ therapy and a potentially predictive power of the MGMT promotor status have to be further explored in larger prospective trials that should also include quality of life assessments.

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