

## Temozolomide as salvage treatment for recurrent intracranial ependymomas of the adult: a retrospective study

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**Background.** Few data are available on temozolomide (TMZ) in ependymomas. We investigated the response, survival, and correlation with MGMT promoter methylation in a cohort of patients with adult intracranial ependymoma receiving TMZ as salvage therapy after failure of surgery and radiotherapy.

**Patients and Methods.** We retrieved clinical information from the institutional database and follow-up visits, and response to TMZ on MRI was evaluated according to the MacDonald criteria.

**Results.** Eighteen patients (median age, 42 y), with either WHO grade III (10) or grade II (8) ependymoma were evaluable. Tumor location at diagnosis was supratentorial in 11 patients and infratentorial in 7. Progression before TMZ was local in 11 patients, local and spinal in 6 patients, and spinal only in one patient. A median of 8 cycles of TMZ (1–24) was administered. Response to TMZ consisted of complete response (CR) in one (5%) patient, partial response (PR) in 3 (17%) patients, stable disease (SD) in 7 (39%) patients, and progressive disease (PD) in 7 (39%) patients. Maximum response occurred after 3, 10, 14, and 15 cycles, respectively, with neurological improvement in 2 patients. All 4 responding patients were chemotherapy naïve. Both anaplastic (2) and grade II (2) tumors responded. Median progression-free survival and overall survival were 9.69 months (95% CI, 3.22–30.98) and 30.55 months (95% CI, 12.85–52.17), respectively. MGMT methylation was available in 11 patients and was not correlated with response or outcome.

**Conclusion.** TMZ has a role in recurrent chemo-naïve adult patients with intracranial ependymoma, regardless of tumor grade and MGMT methylation. We suggest that, after failure of surgery and radiotherapy, TMZ should be considered as a possible first-line treatment for recurrent ependymoma.

**Keywords:** adult ependymomas, MGMT methylation, recurrence, temozolomide.

Intracranial ependymomas are most common in children and rarely arise in adults.<sup>1</sup> About 60% of ependymomas are infratentorial, 40% are supratentorial, and up to 30% are anaplastic (WHO grade III). Regarding treatment strategies for adult intracranial ependymomas, there is a lack of prospective or randomized studies. Few retrospective series are available, and those that are available include a limited number of patients and span several decades during which diagnostic and therapeutic modalities have changed. To date, the optimal management of grades II and III ependymomas includes maximal safe resection, more often followed by limited field radiotherapy.<sup>2–4</sup> Conversely, no role for adjuvant chemotherapy has been

demonstrated so far. A significant proportion of intracranial ependymomas will recur: the dominant pattern of recurrence is at the primary site, and between 10% and 30% (more commonly anaplastic tumors) will develop cerebrospinal fluid spread.<sup>5</sup> Recurrent ependymomas are managed by reoperation whenever feasible,<sup>3,6</sup> reirradiation with increasing use of stereotactic radiotherapy,<sup>7–9</sup> and salvage chemotherapy.<sup>10–12</sup>

A variety of chemotherapeutic drugs and regimens (either platinum based or not) have been employed, but none of them has clearly emerged as superior over the others. Temozolomide (TMZ) may have a role; small series<sup>13</sup> or case descriptions<sup>14–18</sup> have reported some responses in both intracranial

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and spinal ependymomas. However, the number of patients with intracranial ependymomas who have received TMZ so far is limited. Moreover, there are few data on the correlations between response to TMZ and MGMT promoter methylation, which is known to be a major determinant of response/resistance in glioblastomas.<sup>19</sup>

The objective of this study was to investigate the patterns of response and outcome and the correlations with MGMT promoter methylation in a cohort of patients with adult recurrent intracranial ependymomas who received TMZ as salvage chemotherapy.

## Patients and Methods

### Patient Selection and Data Collection

We retrospectively studied all adult patients with recurrent intracranial ependymoma who received TMZ as part of their multimodality treatment between 1999 and 2011 at the Department of Neuro-Oncology of the University Hospital in Turin, Italy. Data pertaining to patient demographics, neurological symptoms, therapeutic management, and outcome were retrieved from the database as well as from clinical notes taken during follow-up visits. The patients who met the following criteria were included into the study: (i) histologically verified intracranial World Health Organization (WHO) grades II and III (anaplastic) ependymomas; (ii) recurrence after surgery and radiotherapy; (iii) measurable enhancing lesion on MRI of at least 1 cm diameter at baseline; (iv) availability of MRI scans before and after chemotherapy (every 2 or 3 cycles) for review; (v) Karnofsky performance score  $\geq 60$ ; (vi) age  $\geq 18$  years. Exclusion criteria were as follows: (i) patients with subependymoma or ependymoblastoma and (ii) patients with spinal ependymoma. All pathology slides were reexamined by one of the authors (P.C.) at the time of the study. The Local Institutional Review Board approved the study.

### Treatment Regimen and Evaluation of Response

TMZ was administered at a dose of 150–200 mg/m<sup>2</sup>/day on days 1–5. A concurrent medication with antiepileptic drugs and/or steroids to control seizures and neurological symptoms and signs was allowed. Treatment with TMZ was repeated every 28 days, provided that all hematologic toxicities from the previous cycles had resolved to  $\leq$ grade 2, and all nonhematologic toxicities had recovered to  $\leq$ grade 1. If recovery had not occurred by day 28, the subsequent cycle of TMZ was delayed until the criteria were met. All toxicities were rated according to the National Cancer Institute (NCI) Common Toxicities Criteria (version 3.0). TMZ dose was reduced by 25% in patients with  $\geq 3$  grade toxicity, and only a single dose reduction was allowed. Patients with persisting grade 3 toxicity after one dose reduction or grade 4 toxicity discontinued TMZ.

Response of tumor on MRI was evaluated according to the MacDonald criteria<sup>20</sup> (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD]) based on changes in tumor size defined as the product of the 2 largest perpendicular diameters on T1-weighted images with contrast medium. MRI images before and after TMZ were reviewed by an investigator (R.S.) blind to patient responses and outcomes.

### MGMT Promoter Methylation Assessment

Genomic DNA was isolated from paraffin sections of tumor tissue, denaturated with sodium hydroxide in a volume of 35 microliters, and subjected to bisulfite treatment in a volume of 350 microliters for 5 hours at 55°C and then purified. The methylation-specific PCR was performed in a 2-step approach.

### Statistical Analysis

The distribution of patients' characteristics was summarized using percentiles for continuous variables and percentages and frequencies for categorical variables.

Overall survival (OS) was defined as the time from the date of TMZ start and the date of death or last follow-up. Progression-free survival (PFS) was defined as the time from the date of TMZ start and the date of progression (disease progression or death) or date of last follow-up.

We estimated survival functions using the Kaplan-Meier method.

A Cox proportional hazard model was used to estimate crude and adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for a set of potential, predefined risk factors for disease progression and mortality. We included in the multivariate analysis only those variables known in the literature as significant prognostic factors. Statistical analyses were performed using Stata 11.2 (StataCorp LP).

## Results

### Patient Characteristics and Initial Treatments

Eighteen of 20 patients were evaluable according to the inclusion criteria. Two patients were excluded because clinical and/or MRI information was incomplete. Patient characteristics and initial treatments are reported in Table 1. Twelve (67%) patients were males, and 6 (33%) were females, with a median age of 42 years (range 18–61y). Ten (56%) patients had a grade III (anaplastic) ependymoma, whereas 8 (44%) had a grade II ependymoma. Tumor location at initial surgery was supratentorial in 11 (61%) patients and infratentorial in 7 (39%). The extent of initial surgery, based either on CT or MRI with contrast medium within 72 hours, consisted of gross total resection in 8 (44.5%) patients, subtotal/partial resection in 8 (44.5%), and biopsy in 2 (11%). Adjuvant conformal radiotherapy with total doses of 50–60 Gy in fractions of 1.8–2.0 Gy was delivered to all patients with grade III ependymoma and to the 4 patients with grade II tumor who underwent incomplete resection. None of the patients received adjuvant chemotherapy.

Treatments at prior relapses before the start of TMZ (Table 1) were heterogeneous and often multiple over time. Seven patients underwent reoperation due to either local intracranial progression (6) or spinal progression alone (1). None of the patients received TMZ adjuvantly after reoperation, and the time intervals between reoperation and start of TMZ ranged between 6 months and 2 years. Ten patients, who had (5) or had not (5) received previous irradiation were treated with radiotherapy: 5 with conformal radiotherapy, 3 with stereotactic radiotherapy, and 2 with cyberknife). Three of 10 patients had a time interval between irradiation and start of TMZ of 3, 6, and 24 months, respectively, and all had PD following TMZ. Four

**Table 1.** Patient characteristics and treatments prior to temozolomide

Patient Number	Sex/Age (y)	Tumor Location	Histology	Surgery	RT (Gy)	Reoperation	Reirradiation (Gy)	Chemotherapy (response)
1	M/18	Supratentorial	II → III	IR	50	GTR	NO	NO
2	M/26	Infratentorial	III	B	50	NO	NO	NO
3	M/28	Infratentorial	III	GTR	60	NO	44 (spine)	NO
4	F/28	Infratentorial	II	IR	54	IR	36 (spine) <sup>a</sup>	Cyclophosphamide + VP-16 + vincristine (SD)
5	M/30	Supratentorial	II	GTR	NO	NO	56	NO
6	M/35	Supratentorial	II → III	GTR	NO	IR	22 <sup>a</sup>	NO
7	M/37	Supratentorial	III	IR	54	IR	NO	NO
8	M/37	Infratentorial	II	IR	58	IR	18 <sup>a</sup>	NO
9	F/41	Infratentorial	II	GTR	NO	GTR	50, 30 (spine) <sup>b</sup>	Cisplatin + VP-16 (SD)
10	F/43	Supratentorial	II	IR	58	IR	16 <sup>a</sup>	PCV (PD)
11	M/42	Supratentorial	II → III	B	56	IR	NO	NO
12	M/42	Supratentorial	III	GTR	50	IR	NO	Cisplatin + VP-16 (PD)
13	M/43	Supratentorial	III	GTR	56	GTR	30 <sup>b</sup>	BCNU (SD)
14	F/51	Supratentorial	II	IR	60	NO	NO	PCV (SD)
15	M/51	Supratentorial	III	GTR	54	NO	NO	NO
16	F/56	Infratentorial	II	GTR	NO	NO	54	NO
17	M/56	Infratentorial	II	GTR	NO	NO	56	NO
18	F/61	Supratentorial	III	IR	54	NO	NO	NO

Abbreviations: B, biopsy; F, female; GTR, gross total resection; IR, incomplete resection; L, left; M, male; R, right; RT, radiation therapy; y, years; NO, not done.

<sup>a</sup>Stereotactic radiotherapy.

<sup>b</sup>Cyberknife.

patients with SD and one with PR following TMZ had a time interval from last irradiation ranging between 6 months and 5 years. One patient with SD and one with PR following TMZ had a time interval from last irradiation of one month and 3 months, respectively. Six out of 18 (33%) patients received chemotherapy with cisplatin + VP-16 (2), PCV (2), BCNU (1), and cyclophosphamide + VP16 + vincristine (1) and displayed 4 SDs and 2 PDs. Twelve of 18 (67%) patients were chemotherapy naïve at the time of TMZ treatment.

### Response, Progression-free Survival, and Overall Survival Following Temozolomide

Patients' characteristics, responses, and outcomes related to TMZ treatment are reported in Table 2.

Type of progression on MRI before TMZ was local in 11 (61%) patients, local and spinal in 6 (33%), and spinal alone in one (6%). Patients presented at the time of tumor recurrence before TMZ with the following symptoms and signs: headache (5 patients), seizures (4 patients), motor deficit (7 patients), gait ataxia (2 patients), and homonymous hemianopsia (one patient). Three patients were asymptomatic. Patients' performance status using the Karnofsky scale ranged between 60 and 90 (median, 70).

The median time to initiation of TMZ after initial surgery was 28 months (range, 6–156 mo). A total of 170 cycles of TMZ were administered with a median of 8 cycles per patient (range, 1–24).

Best response on MRI to TMZ was as follows: CR in one of 18 (5%) patients (Fig. 1) and PR in 3 of 18 patients (17%) (Figs 1

and 2) with an overall response rate of 22%; SD in 7 of 18 patients (39%) and PD in 7 of 18 patients (39%). Maximum response was observed after 3, 10, 14, and 15 cycles, respectively. Two out of 4 responding patients (one CR and one PR) derived significant neurological improvement. Among the 12 patients who were chemotherapy naïve, 4 (33%) displayed a response (1 CR + 3 PR) to TMZ, while none of the 6 patients who received prior chemotherapy had a response (3 SDs and 3 PDs). Response to TMZ occurred in both grades III (2) and II (2) tumors. MGMT status was available in one of 4 responding patients (a PR), and was unmethylated among the 5 patients with SD. MGMT promoter was unmethylated in 3 and methylated in 2, respectively. Among the 5 patients with PD, MGMT promoter was unmethylated in 2 and methylated in 3, respectively.

All 4 responding patients had a local intracranial failure before TMZ. Of the 6 patients with spinal progression alone (1) or associated with local intracranial failure (5) before TMZ, 3 patients displayed a PD and 3 a SD.

Median PFS was 9.69 months (95% CI, 3.22–30.98) and ranged between one month and 153 months (Fig. 3). PFS at 6, 12, and 18 months was 66.67% (95% CI, 40.35–83.43), 50% (95% CI, 21.58–65.12), and 38.89% (95% CI, 13.65–54.54), respectively. PFS at 5 and 10 years was 11.11% (95% CI 1, 1.86–29.75). PFS of the patient with CR was 153 months, while PFS of the 3 patients with PR was 9, 60, and 113 months, respectively. One patient, who displayed a PR after 14 cycles and was MGMT unmethylated, is still free of tumor progression at 113 months. PFS of the 7 patients with SD ranged between 6 and 56 months (median, 18 mo). One patient with SD is still

**Table 2.** Patient characteristics, response, and outcome related to temozolomide

Patient	Progression <sup>a</sup>	KPS <sup>b</sup>	No. of Cycles	Timing	Response	MGMT Promoter	PFS (mo)	Salvage Treatments (response)	OS (mo)
1	Local	70	6	1st line	PD	Unmethylated	2	SRT (PD)	22
2	Local	60	18	1st line	CR	–	153	Reoperation	161+
3	Spinal	70	3	1st line	PD	–	3	Cyclophosphamide (PD)	18
4	Local + spinal	90	6	2nd line	PD	Methylated	3	Reoperation + Carboplatin	32
5	Local	80	6	1st line	SD	–	6	NO	11
6	Local + spinal	60	2	1st line	PD	–	2	NO	3
7	Local	70	5	1st line	PD	Methylated	5	Etoposide + Cisplatin (SD)	17
8	Local	80	16	1st line	PR	–	60	SRT (SD)	84+
9	Local + spinal	90	5	2nd line	SD	Methylated	43	SRT (SD)	55
10	Local	60	3	2nd line	PD	Methylated	3	NO	5
11	Local + spinal	60	12	1st line	SD	Methylated	12	NO	16
12	Local + spinal	80	1	2nd line	PD	Unmethylated	1	NO	3
13	Local	80	15	2nd line	SD	Unmethylated	18	Reoperation + SRT + Etoposide (SD)	120+
14	Local	60	12	2nd line	SD	–	56+	No relapse	56+
15	Local	90	9	1st line	PR	–	9	SRT + Etoposide (PD)	30
16	Local	80	9	1st line	SD	Unmethylated	9	Etoposide (SD)	39
17	Local	80	24	1st line	PR	Unmethylated	113+	No relapse	113+
18	Local + spinal	70	18	1st line	SD	Unmethylated	30	NO	49

Abbreviations: CR, complete response; mo, months; PD, progressive disease; PR, partial response; SD, stable disease SRT, stereotactic radiotherapy; NO, not done.

<sup>a</sup>Before temozolomide.

<sup>b</sup>Karnofsky Performance Score.

free of tumor progression after 56 months. PFS of the 7 patients with PD ranged between one and 5 months (median, 3 mo).

Median OS was 30.55 months (95% CI, 12.85–52.17) and ranged between 3 months and 161 months (Fig. 3). OS at 6, 12, and 18 months was 83.33% (95% CI, 56.77–94.30), 77.78% (95% CI, 51.10–91.02), and 61.11% (95% CI, 35.32–79.21), respectively. OS at 5 and 10 years was 22.2% (95% CI, 6.91–42.88). The patient with CR is still alive after 161 months, while among the patients with PR, 2 are still alive after 84 and 113 months, respectively, and one died after 30 months. OS of the 7 patients with SD ranged between 11 and 120 months (median, 49 mo). OS of the 7 patients with PD ranged between 3 and 32 months (median, 17 mo). All patients with PD have died.

None of the clinicopathological factors (sex, age, histology, tumor location, type of initial surgery, reoperation, Karnofsky score, MGMT promoter status, and timing of TMZ) were significantly associated with response, PFS, or OS. The statistical comparison in terms of PFS and OS between patients who received TMZ at first- or second line was hampered by the fact that the number of patients who received TMZ at second line was too small (only 6 patients). It is clear that not all patients receiving TMZ at second line had a uniformly bad outcome, as 3 of the 6 patients displayed PFS following TMZ of at least 12 months. In terms of OS, 4 of 6 patients who received TMZ at second line survived more than 12 months compared with 10 of the 12 patients who received TMZ as first-line treatment.

Patterns of progression on MRI after failure of TMZ did not change, except for the patient with an infratentorial tumor

who displayed a CR following TMZ. At failure after 153 months, this patient displayed an intracranial leptomeningeal spread without local progression.

At failure following TMZ, 6 patients received supportive care only, while 10 received different salvage treatments (Table 2). Five of 10 patients underwent stereotactic radiotherapy only (2 SD and one PD) or associated with chemotherapy (one SD, one PD). Three patients received chemotherapy alone, and 2 of them had stabilization with etoposide with or without cisplatin, and one had a PD. Three patients underwent reoperation, and one of them was also given carboplatin.

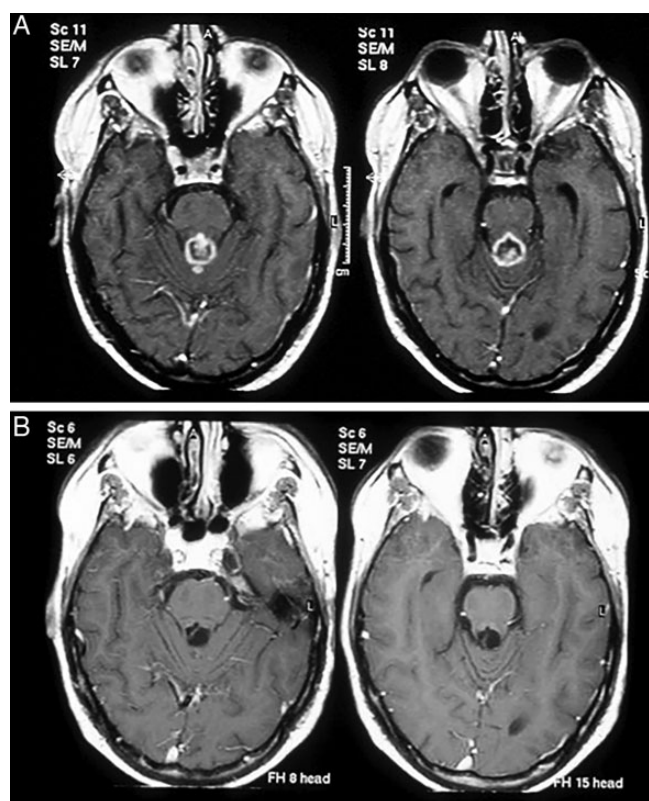
### Toxicity

Toxicity was evaluated using the NCI Common Toxicity Criteria (version 3.0). The following TMZ-related toxicities were observed: leukopenia in 7 patients (grade I in one; grade II in 3; grade III in 3); thrombocytopenia in 6 patients (grade II in one; grade III in 5). We did not observe any case of febrile neutropenia or treatment-related death. Two patients discontinued TMZ for grade 4 (one) and persistent grade III (one) myelotoxicity after one and 5 cycles, respectively.

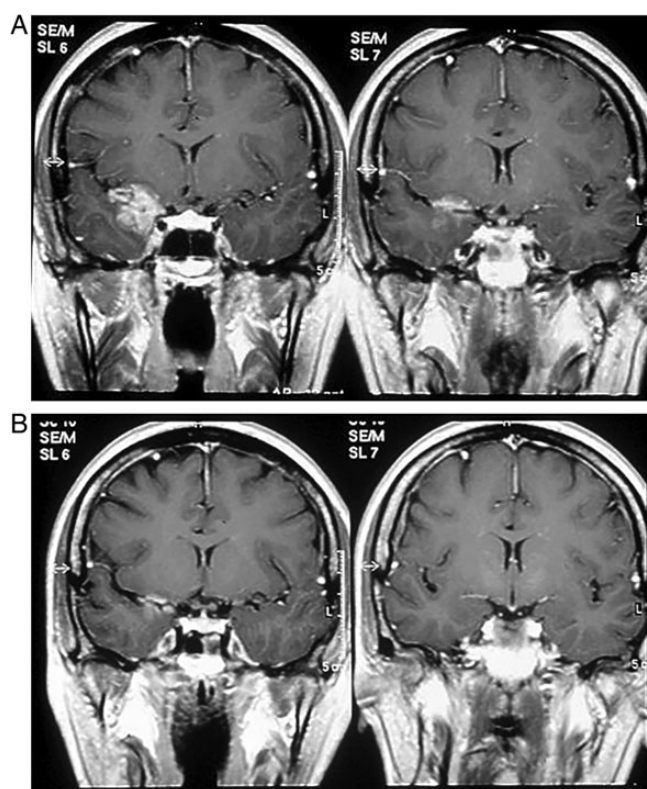
### Discussion

The management of adult patients with recurrent intracranial ependymoma is challenging because they often have an unpredictable course with multiple relapses and eventual death in most cases. Because of the rarity of the disease, there is a





**Fig. 1.** 26-year-old male patient with infratentorial anaplastic ependymoma, recurrent after biopsy and adjuvant radiotherapy. Contrast-enhanced T1-weighted MRI: (A) Before temozolomide; (B) after 15 cycles of temozolomide, showing a complete response.



**Fig. 2.** 51-year-old male patient with supratentorial anaplastic ependymoma, recurrent after gross total resection and adjuvant radiotherapy. Contrast-enhanced T1-weighted MRI: (A) Before temozolomide; (B) after 10 cycles of temozolomide, showing a partial response.

paucity of available literature; however, despite a lack of randomized clinical trials, there is a general consensus on timing of the different treatment options. Reoperation with attempted gross total resection of the tumor should be considered first, even if there is more than one site of recurrence.<sup>12,21</sup> When a recurrent lesion is inoperable, radiotherapy should be offered to both previously nonirradiated and irradiated patients. In these latter cases, either stereotactic radiosurgery<sup>7</sup> or conventional external beam radiotherapy can be used,<sup>9</sup> depending on previous doses, fractionation, and response. All of these considerations apply to our series.

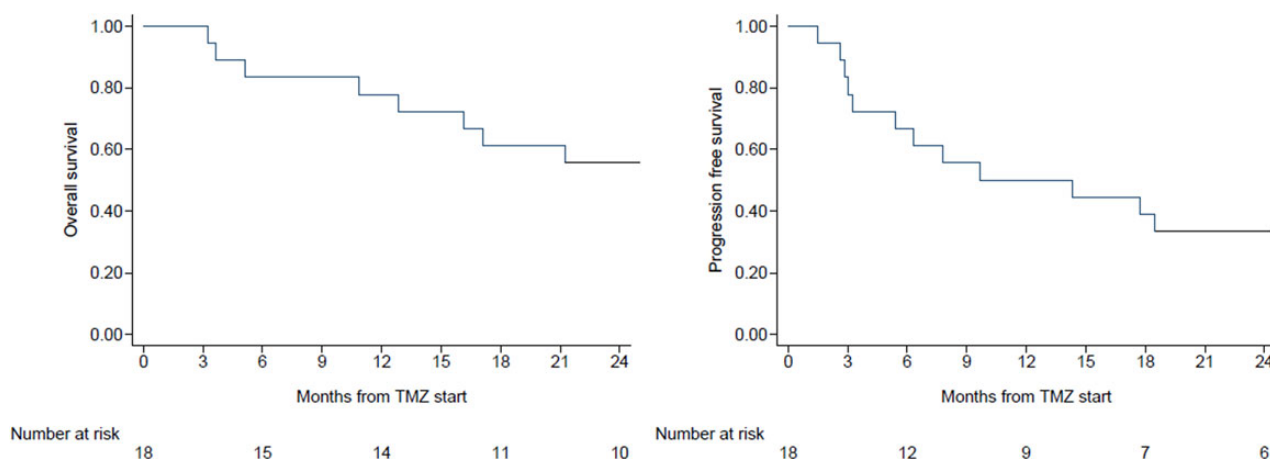
Chemotherapy is reserved as a salvage treatment for patients failing reoperation and/or reirradiation. To date, only two retrospective series have been reported focusing on recurrent intracranial ependymomas of the adult.<sup>11,13</sup> Another series has included pediatric patients and spinal tumors as well.<sup>10</sup> Platinum-based regimens seem more effective than regimens without a platinum agent in terms of response but not PFS or OS,<sup>10,11</sup> while TMZ in the standard schedule has been reported in a retrospective study<sup>13</sup> and a few case reports<sup>14–18</sup> (Table 3).

The results of the present series are comparable with those reported by Brandes et al<sup>11</sup> in terms of response (PR + CR of 22% vs 21.4%) and PFS (median 9.69 vs 9.9 months, at 6 months 66.67% vs 71%, and at 12 months 50.00% vs 44.3%). The median OS of our series (30.55 months) was

somewhat lower than that of 40.7 months reported by Brandes et al<sup>11</sup>; however, OS at 12 months was similar (77.78% vs 73%). Conversely, our results are significantly superior over those reported by Chamberlain and Johnston<sup>13</sup> with the same regimen of TMZ in terms of response rate (22% vs 4%), median PFS (9.69 vs 2 months), PFS 6 (66.7% vs. 2%), and OS (30.55 vs 3 months). Two facts could at least partially explain this difference: all patients in the series of Chamberlain and Johnston were pretreated with cisplatin-based chemotherapy, while 67% (12/18) patients in this series were chemotherapy naïve and thus received TMZ in a less advanced phase of the disease (median time to initiation of TMZ 28 vs 46 mo). Second, it is likely that the series of Chamberlain and Johnston included patients with more aggressive disease. In this regard, supratentorial tumors that were associated with a worse outcome<sup>3,22–26</sup> represented 100% of their series compared with 61% (11/18) patients only in this series.

One patient in our series had a CR lasting 13 years: the possibility of achieving CRs following TMZ was previously suggested by 2 case descriptions,<sup>14,15</sup> and one of these patients was in remission for 10 years after completing the treatment.<sup>14</sup> Interestingly, some responses to TMZ have been reported in relapsed ependymoma of childhood as well.<sup>27</sup>

This study reports novel data. First, the response to TMZ can often be delayed. In 3 of 4 responding patients, response



**Fig. 3.** Kaplan-Meier curves for progression-free survival (PFS) (A) and overall survival (OS) (B) of the entire series. Median PFS was 9.69 months (95% C.I., 3.22–30.98). Median OS was 30.55 months (95% C.I., 12.85–52.17).

**Table 3.** Chemotherapy for recurrent ependymomas in the adult: literature review

Author	No. of patients	Tumor location	Histology	Regimen	Response	TTP (mo)	OS (mo)
Gornet et al, 1999 <sup>a</sup>	16	Intracranial and spinal	Grades II and III	Platinum-based	PR/MR 67% SD 33%	6	NR
				Nitrosourea-based	PR/MR 25% SD 50%	10	NR
				Miscellanea	PR/MR 11% SD 56%	3	NR
Brandes et al, 2005	28	Intracranial	Grades II and III	Platinum-based	CR 15.4% PR 15.4% SD 53.58%	9.9	31
				on platinum-based	CR 0 PR 13.3% SD 73.3%	10.9	40.7
Chamberlain and Johnston, 2009	25	Supratentorial	Grade II	TMZ	CR 0 PR 4% SD 36%	2 <sup>b</sup>	3 <sup>c</sup>
Present series	18	Intracranial	Grades II and III	TMZ	CR 5% PR 17% SD 39%	9.69	30.55

Abbreviations: CR, complete response; mo, months; NR, not reported; OS, overall survival; PR, partial response; SD, stable disease; TMZ, temozolomide; TTP, time to progression.

<sup>a</sup>Some pediatric patients included.

<sup>b</sup>Range, 1–7 months.

<sup>c</sup>Range, 2–8 months.

NR, Not reported.

started after 6 cycles and was cumulative over time. Second, responses to TMZ have been observed in chemotherapy-naïve patients only. Interestingly, we treated 7 patients who had spinal metastases with TMZ; none of these patients had a response on MRI, and we observed 3 SDs and 4 PDs. In this regard, it must be stressed that the MRI evaluation of changes in tumor size from leptomeningeal metastases following chemotherapy, either systemic or intrathecal, is difficult and challenging. This was recently reported by the RANO group in a position

paper on neoplastic meningitis from solid and hematologic tumors.<sup>28</sup>

It is well known that the methylation of the MGMT gene promoter is predictive of response to TMZ in glioblastomas<sup>19,29,30</sup>; however, it is rarely methylated in pediatric ependymomas,<sup>31,32</sup> and there is a lack of information on the correlations between MGMT promoter methylation and response to TMZ in both pediatric and adult patients. To our knowledge, this is the first study that has analyzed MGMT gene promoter status in a

cohort of patients with intracranial ependymomas of the adult, who were homogeneously treated and evaluated for response and outcome following TMZ. Among 11 of 18 patients whose MGMT methylation status was available, we did not observe any correlation with response and outcome. Interestingly, one patient with PR and 2 patients with SD of long duration were unmethylated. This suggests that the response to TMZ in ependymomas could occur regardless of MGMT methylation status and depend on other unknown biological factors.

There could be some concern about patients who underwent reirradiation before TMZ and whose imaging changes (defined as response or SD) were at least partially attributable to the radiation itself and not to TMZ chemotherapy. However, this could be the case in only 2 patients only who received radiotherapy shortly before TMZ (one month and 3 months, respectively) and who displayed SD and PR following TMZ.

We cannot exclude that prior chemotherapy could have influenced the likelihood of response to subsequent TMZ. Of the 4 patients who had SD following the chemotherapy prior to TMZ, 3 of them displayed SD after TMZ as well. However, this seems unlikely because none of these 4 patients was switched to TMZ while showing the SD. Moreover, previous chemotherapy was interrupted at different time points, and the interval between the interruption of previous chemotherapy and relapse before the start of TMZ ranged between 6 months and 2.5 years.

Several patients have survived an extensive time after failure of TMZ. Salvage treatments, in particular stereotactic radiotherapy and reoperation, seem to have contributed to prolonged survival, while the impact of chemotherapeutic drugs such as etoposide or cisplatin seems less important. In this regard, it must be acknowledged that some patients could have been treated with reirradiation before receiving TMZ. Furthermore, an inherent indolent course of disease cannot be excluded in some patients.

This study has several limitations. It is a retrospective analysis, and the data were collected over a relatively long time period. Moreover, the sample size is too small to preclude any meaningful statistical analysis. In this regard, PFS values of patients who responded, had SD, or had PD, respectively, are clearly different, but the numbers are too small to achieve statistical significance.

Future prospective studies should explore the role of alternative regimens of TMZ and targeted agents, alone or in combination. In this regard, a small retrospective study has suggested an activity of bevacizumab,<sup>33</sup> and a phase 2 study by the CERN consortium on the combination of dose-dense TMZ and lapatinib (a molecular agent targeting ErbB1 and ErbB2), has concluded accrual, and the preliminary results were presented<sup>34</sup> in November 2014 at the Annual Meeting of the Society for Neuro-Oncology. Among 19 intracranial tumors, the median PFS and PFS at 6 and 12 months were 24 weeks, 43%, and 29% for supratentorial tumors and 21 weeks, 40%, and 20% for infratentorial tumors, respectively. Preliminary gene expression analysis correlated the response with higher ErbB2 mRNA expression.

In conclusion, our study suggests that TMZ has a role in recurrent chemotherapy-naïve adult patients with intracranial ependymoma, both in terms of response and improved outcome. MGMT methylation status does not seem to play a major role in influencing response. Based on these data, we

suggest that TMZ should be considered in clinical trials and/or daily clinical practice as a possible first-line chemotherapy agent for adults with recurrent intracranial ependymomas who have failed reoperation and/or reirradiation.

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*Conflict of interest statement.* None declared.

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