Original article

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Effect of pregabalin add-on treatment on seizure control, quality of life, and anxiety in patients with brain tumour-related epilepsy: a pilot study

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ABSTRACT – *Objective*. An open pilot study to evaluate the effect of pregabalin (PGB) as add-on therapy on seizure control, quality of life, and anxiety in patients with brain tumour-related epilepsy (BTRE). *Materials and methods*. We recruited 25 consecutive patients with BTRE and uncontrolled seizures. At baseline and during follow-up, patients underwent a complete physical and neurological examination and were evaluated using the QOLIE 31P (V2), EORTC QLQ C30, Adverse Events Profile, and Hamilton Anxiety Rating Scale (HAM-A). At baseline, a seizure diary was given. *Results*. During follow-up, 17 patients underwent chemotherapy, none underwent radiotherapy, 9 had disease progression, and 3 died. Mean duration of follow-up was 4.1 months. Mean PGB dosage was 279 mg/day. At baseline, mean weekly seizure frequency was 5.3 (±10) and at last available follow-up visit was 2.8±5. This difference was statistically significant (p=0.016). The responder rate was 76%. Ten patients dropped out; 4 as a result of seizure worsening, 1 as a result of unchanged seizure frequency, 3 as a result of a lack of compliance, and 2 as a result of side effects. Based on the QOLIE-31-P, a significant improvement of the subscale "seizure worry" (p=0.004) and a significant decrease in distress scores related to AEDs and social life (p=0.009 and p=0.008, respectively) were observed. A significant decrease in HAM-A score (p=0.002) was documented. *Conclusions*. These data indicate that PGB may represent a valid alternative as add-on treatment in this patient population, based on its efficacy on seizure control and anxiety.

Key words: anxiety, brain tumor, efficacy, epilepsy, pregabalin, quality of life

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Brain-tumour related epilepsy (BTRE) presents a host of problems for many reasons. First, BTRE is often refractory to pharmacological therapies (Löscher and Potschka, 2005; Baltes *et al*., 2007; Luna-Tortós *et al*., 2008) and second, it strongly affects quality of life (QoL) because it imposes an unpredictability of seizure occurrence and long-term assumption of additional medication (Rossetti and Stupp, 2010). In addition, antiepileptic drugs (AEDs) can cause possible side effects together with those already known to systemic treatment (Vecht and van Breemen, 2006) and can interact with systemic therapies. The fact that classical AEDs can affect the efficacy of oncological therapies, through the modification of their hepatic metabolism, is well known in the literature (Oberndorfer *et al*., 2005), while data concerning the effect of the more recent AEDs on these therapies are scarce (Wen and Marks, 2002; Vecht *et al*., 2003; Perucca, 2005; Singh *et al*., 2007; van Breemen *et al*., 2007; Yap *et al*., 2008). For these reasons, many authors recommend AEDs that do not modify hepatic metabolism (Vecht *et al*., 2003; Singh *et al*., 2007). Finally, to date, it is not clear whether new AEDs are influenced by chemotherapy (Pace *et al*., 2003; Ngo *et al*., 2006).

Pregabalin (PGB) is a new AED used as add-on treatment in epilepsy (French *et al*., 2003). PGB exhibits a linear pharmacokinetic profile, a lack of protein binding, a lack of hepatic metabolism, and is eliminated by renal excretion. No drug interactions have been observed between PGB and other AEDs (Brodie *et al*., 2005) and it does not seem to interfere with chemotherapy (Carreño *et al*., 2007). Adverse events related to somnolence, fatigue, dizziness, and diplopia are dose-dependent and usually mild (Rossetti and Stupp, 2010). PGB has also been shown to be effective against seizures in refractory epilepsy (Carreño *et al*., 2007) and a recent, small, retrospective study on nine patients with BTRE (Novy *et al*., 2009) showed a seizure reduction of 50%, with 6 patients seizure-free.

Finally, recent studies demonstrate that PGB is efficacious in generalised anxiety disorder with a consistent effect on physic and somatic anxiety symptoms (Stein, 2007; Montgomery *et al*., 2008). This makes it eligible for patients with anxiety symptoms, such as patients with cancer (Bandelow *et al*., 2007; Owen, 2007). On the basis of these data in the literature, PGB may be helpful for both the control of seizures and symptoms (such as anxiety) that decrease QoL of BTRE patients. To date, PGB therapy in patients with BTRE has not been studied extensively. Therefore, we conducted an open, before-after pilot study to evaluate the effect of PGB as add-on therapy on seizure control, QoL, and anxiety in patients with BTRE.

Materials and methods

Primary aim

To evaluate the effect of PGB on seizure control as add-on treatment in 25 patients with BTRE. The primary outcome variable was the mean number of weekly seizures after six months of treatment. Efficacy variables included: 1) rate of seizure freedom at last available follow-up visit for each patient, relative to baseline; 2) responder rate (a patient responder is defined as a patient having achieved at least a 50% weekly seizure reduction during the treatment, relative to seizure frequency [SF] at baseline); and 3) reduction in SF, relative to baseline period. SF was evaluated as mean weekly SF during the treatment period.

Secondary aims

To evaluate: 1) the impact of PGB on QoL and anxiety at the last available follow-up visit (at three or six months), relative to baseline; 2) the possible modification of anxiety evaluated by tests at the last available follow-up visit (at three or six months), relative to baseline; and 3) whether disease progression (evaluated by radiological examination) modifies seizure outcome and responses to psychological tests.

Patients

We recruited patients with BTRE who had received standard AED therapy and who had had at least one seizure in the month preceding recruitment, even though AEDs were at the maximum tolerable dose.

Some patients underwent chemotherapy and/or radiotherapy prior to their first visit at our centre. The stage of disease and therapy prior to coming to our centre did not influence our therapeutic approach to seizure control. All patients were treated with the current standard care for patients with brain tumours. PGB was added as a first or second add-on drug at 75 mg/day to the following specific drugs: clobazan, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, valproate, and topiramate. Patients with Karnofsky Performance Status <60, Mini Mental State Examination <24, epilepsy prior to tumour onset, other neurological or psychiatric disease, or receiving therapy with gabapentin were excluded from recruitment. At the first visit, we performed an initial screening with neurological examination (described below) and SF calculation for the 30 days prior to recruitment into the study. A seizure diary was delivered to the patient in order to have an objective tool for checking weekly SF. At one month, three months, and six months, patients

underwent complete physical and neurological examination, assessment of SF, and evaluation of adverse events (by observation or spontaneous reports). Tests were given only after three and six months.
The seizure count was made on the basis of an historical report (for baseline SF), seizure diary, and direct contact with the patients or caregivers during follow-up. To validate seizure occurrence, patients were asked to call the study centre after each seizure episode. This interim contact was recorded and compared with questionnaire responses.
All patients who showed stable SF or worsening of SF (with respect to baseline) during treatment period, with PGB at maximum tolerated doses and who should be considered for an additional AED, were regarded as treatment failures and analysed as such (*i.e.* SF was considered to be equal to that at study entry).
This study was approved by the Ethical Committee of our institute and patients gave their informed consent.

Pregabalin administration

PGB was used as first or second add-on therapy (second add-on therapy is defined as the AED added after failure of first monotherapy and first add-on drug) at a variable dosage of 150 to 600 mg/die. The starting dosage was 75 mg/die with an increasing schedule up to the maximum dosage of 600 mg/day over four weeks (depending on seizure control and eventual onset of adverse events).

Safety variable

The presence of adverse events similar to those observed in the literature (French *et al.*, 2003) were evaluated using the "Adverse Events Profile" (AEP) test (Gilliam *et al.*, 2004) and by spontaneous report or observations.

Evaluation of adverse events

An "adverse event" (AE) is any unfavourable and unintended sign, symptom or disease, temporally associated with a medical treatment or procedure, that may or may not be considered to be related to the medical treatment or procedure itself. All adverse events were classified utilising the Common Terminology Criteria for Adverse Events; the Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events v3.0, DCTD, NCI, NIH, DHHS (2003). Progression of disease was not considered an AE. All patients who had taken at least one dose of drug were included in the analysis of toxicity. Spontaneously reported or observed AEs were recorded along with details regarding time of onset and resolution, intensity, need for concomitant of treatment, and the investigator's opinion of the relationship with study treatment.

QOL and other instruments

The Karnofsky Performance Status evaluates survival and provides information about the patients' functional status (Karnofsky *et al.*, 1951). The Barthel index registers 10 activities of daily life (Mahoney and Barthel, 1965). The MMSE is a brief, standardised tool to grade patients' cognitive function (Folstein *et al.*, 1975). The Adverse Events Profile Test is used to evaluate the presence and severity of symptoms in patients treated with AEDs (Gilliam *et al.*, 2004). The Quality of life in Epilepsy Inventory QOLIE 31P(V2) (Cramer *et al.*, 2003) is a 31-item self-administered questionnaire designed to be completed by epileptic patients alone. The Quality of Life in Cancer EORTC QLQ-C30 (Apolone *et al.*, 1998) is a cancer-specific, self-administered, structured questionnaire designed for use in clinical trials. The Hamilton Anxiety Scale (HAM-A) assesses somatic and psychic anxiety (Hamilton, 1959). The Zung Self Depression Rating Scale is a self-administrated test for depression (Giovagnoli, 1999; Zung, 1965).

Sample size

Given the pilot character of our study, we considered that a reasonable approach for the evaluation of PGB was to recruit 25 patients who had been part of other patient groups with seizure disorders. We expected a 20% drop-out rate (n=5) for a total of 20 patients included in the study. Considering the predetermined sample size, we calculated the expected effect size based on the primary outcome variable; the mean number of weekly seizures. We applied a one-sided paired T-test because we expected to observe a decrease of the mean number of seizures between the baseline and the follow-up values. This is appropriate for the pilot nature of the study. Furthermore, we hypothesized: 1) a weekly mean frequency at baseline equal to 0.58 (French *et al.*, 2003), calculated from the SF over the month prior to baseline visit; and 2) a standard deviation equal to 0.81 (French *et al.*, 2003). A sample size of 20 allowed us to detect a reduction of the mean seizure frequency equal to 83% (weekly mean frequency at follow-up equal to 0.10 at visit 4 and an effect size equal to 0.56), achieving a statistical power of 80% and a significance level of 5%. Similar reductions were seen with n=21 using the Wilcoxon test for paired data for non-normally distributed data.

Statistical analysis

We computed descriptive statistics for all variables of interest. Continuous data were reported as mean

and standard deviation and we represented categorical data with frequencies and percentage values. We performed an intention-to-treat (ITT) analysis taking into account that all patients took at least one dose of PGB. To compare mean scores at different times we used the T-test for paired data and Wilcoxon test, when appropriate, considering a p value <0.05 as statistically significant. In order to assess the relationships between categorical variables, we employed the Pearson's Chi-squared test of independence and the McNemar test, when appropriate. All statistical analyses were performed with SPSS statistical software version 18 (SPSS Inc., Chicago IL, USA).

Results

Patient profiles

Twenty-five patients with BTRE were followed for six months (*table 1*). The mean dosage of PGB was 279 mg/day (min 75 mg/day; max 600 mg/day). During follow-up, 17 patients received chemotherapy and none underwent radiotherapy. No patients were taking psychotropic drugs and 14 took steroids. Four patients dropped out due to worsening of seizures (16%), 1 with unchanged SF (4%), 3 due to a lack of compliance, and 2 due to side effects. Nine patients had disease progression during follow-up and 3 patients (12%) died. At the end, 12 patients (48%) completed the six-month follow-up. Mean follow-up period was 4.1 months (min 1; max 6).

Efficacy

Seizure freedom

At the end of follow-up, in the whole ITT population, we observed: 9 patients who were seizure-free (36%), 10 patients with a seizure reduction >50% (40%), 2 patients who were unchanged (8%), and 4 patients with seizure worsening (16%). Responder rate in the ITT population was 76%. The statistical analysis of the ITT population (n=25) showed a significant difference in presence/absence of seizures between the baseline and the final follow-up visit calculated by the McNemar Test (p=0.004) (*data not shown*).

At the end of follow-up, for the patients who completed the six-month follow-up (n=12; 48%), we observed: 5 patients who were seizure-free (41.7%), 6 patients with a seizure reduction >50% (50%), and 1 patient who was unchanged (8.3%). Responder rate was 91.7%.

Mean reduction of weekly SF

In the ITT population (n=25) at baseline, all patients had seizures in the previous month with a mean weekly SF of 5.3 ($\pm$10) and at the last available follow-up visit, patients had a mean weekly SF of 2.8$\pm$5 (p=0.016) (*data not shown*).

The statistical analysis of patients who had completed the six-month follow-up period (n=12; 48%) showed a significant reduction in the number of mean weekly seizures between the baseline (5.67$\pm$13.7) and final follow-up visit (0.58$\pm$0.99) (p=0.003) (*data not shown*).

The Wilcoxon test which examined the mean weekly SF before and during follow-up in the two groups separately (stable disease: 16 patients; disease progression: 9 patients) showed a significant reduction in mean weekly SF only in the group with stable disease (p=0.012) (*data not shown*).

Finally, we evaluated the efficacy of PGB in the ITT population and we divided the whole population into two groups according to seizure type: simple partial/complex partial (12 patients) and simple partial/complex partial+secondary generalised tonic-clonic (13 patients). In the first group, we observed: 3 patients who were seizure-free (25%), 5 with a seizure reduction >50% (41.7%), 3 who had seizure worsening (25%), and 1 who was unchanged (8.3%). In the second group we observed: 6 patients who were seizure-free (46.2%), 5 with a seizure reduction >50% (38.5%), 1 who was unchanged (7.7%), 1 one who had seizure worsening (7.7%).

Side effects

Two patients (8%) dropped out due to significant side effects (Grade 3 of CTCAE); 1 with dizziness and 1 with irritation and dryness of the eye (*table 1*). No other side effects were observed.

Evaluation of tests

By comparing between baseline and last available follow-up visit for each patient in the whole group (*table 2*), we found no significant difference in: KPS, BI, MMSE, EORTC-QLQ-C30, AEP, or ZSDRS. On the other hand, we found a significant improvement of the subscale "seizure worry" of QOLIE-31-P (p=0.004), a significant decrease in the distress scores related to AEDs and social life (p=0.009 and p=0.008, respectively), and a significant decrease in HAM-A score (p=0.002). For the group of patients who had stable radiological disease (n=16) and in the group of patients who had radiological disease progression (n=9), we compared each patient separately at baseline and at the last available follow-up visit. We found no significant difference in KPS, BI, MMSE, EORTC-QLQ-C30, AEP, or ZSDRS in patients who had stable radiological disease. On the other hand, in these patients, we observed a significant improvement of the subscale "seizure worry" of

Table 1. Patient clinical characteristics.

	Age (yrs)	Sex	Histology	Surgery	CT	Steroids	Seizure type	Baseline AED therapy (mg/day)	PGB dose assigned (mg/day)	Duration of therapy with PGB (months)	No. of seizures in the month before entering the study	No. of seizures during follow-up	Efficacy	SE	Reasons for drop out	DP	Dead
1	58	F	MEN	GTR	NO	NO	SP	TPM 300	300	6	12	26	>50%		-	NO	NO
2	40	M	AO	GTR	NO	NO	CP	LTG 500 LEV 3000	150	6	4	24	Unchanged		-	NO	NO
3	42	M	GC	Biopsy	TMZ	YES	SP	OXC 1800	600	1	60	90	W		Seizures	NO	NO
4	64	F	GC	Biopsy	TMZ	YES	CP+SGTC	LEV 3000	150	6	4	6	>50%		-	NO	NO
5	32	M	AO	GTR	FTMU	YES	CP+SGTC	TPM 400	150	1	4	16	W		Seizures	YES	NO
6	46	M	AA	PR	FTMU	YES	SP	LEV 3000	150	3	4	0	Seizure freedom	Dizziness	SE	NO	NO
7	36	M	GBM	PR	TMZ	YES	SP	OXC 1800	600	6	4	5	>50%		-	YES	NO
8	64	M	LGA	Biopsy	NO	NO	SP	LEV 3000 VPA 2000	600	6	45	24	>50%		-	NO	NO
9	46	M	AA	PR	TMZ	NO	SP	OXC 1800	300	4	4	18	W		Seizures	NO	NO
10	36	M	MET (melanoma)	NO	FTMU	YES	SP	OXC 1200	225	6	5	0	Seizure freedom		-	YES	NO
11	41	M	AOA	PR	TMZ	NO	SP+SGTC	LTG 400 OXC 1800	225	6	4	0	Seizure freedom		-	YES	NO
12	38	F	AA	PR	FTMU	YES	SP+SGTC	LEV 3000	225	1	60	30	>50%		-	YES	YES
13	31	M	AO	Radio-surgery	NO	YES	SP	TPM 500 OXC 1200	300	1	60	30	>50%		No co-operation	NO	NO
14	69	F	MEN	GTR	NO	NO	SP	OXC 600	150	6	210	90	>50%		-	NO	NO
15	72	F	GBM	PR	TMZ	YES	SP+SGTC	PB 150	150	3	3	1	>50%		-	YES	YES
16	62	M	GBM	PR	TMZ	YES	CP+SGTC	OXC 1800	225	6	2	0	Seizure freedom		-	NO	NO

Table 1 (*Continued*)

	Age (yrs)	Sex	Histology	Surgery	CT	Steroids	Seizure type	Baseline AED therapy (mg/day)	PGB dose assigned (mg/day)	Duration of therapy with PGB (months)	No. of seizures in the month before entering the study	No. of seizures during follow-up	Efficacy	SE	Reasons for drop out	DP	Dead
17	37	M	AA	PR	TMZ	NO	SP	VPA 1000	600	3	18	180	W		Seizures	YES	NO
18	34	M	AOA	PR	NO	NO	CP+SGTC	LTG 400 LEV 3000 VPA 1000	300	3	30	90	Unchanged		Seizures	NO	NO
19	60	M	GBM	Biopsy	TMZ	NO	CP+SGTC	PB 100	150	6	2	0	Seizure freedom		-	NO	NO
20	54	F	GBM	PR	TMZ	YES	CP+SGTC	LEV 3000	150	6	2	0	Seizure freedom		-	NO	NO
21	60	M	MET (lung)	GTR	NO	YES	SP	OXC 600	75	1	3	0	Seizure freedom	Irritation and dry eye	SE	NO	NO
22	37	M	AOA	PR	FTMU+Beva-cizumab	YES	SP+SGTC	LEV 3000 CNZ 4	600	3	12	0	Seizure freedom		-	YES	YES
23	19	F	LGA	PR	NO	NO	CP+SGTC	LEV 3000	300	3	1	0	Seizure freedom		No co-operation	NO	NO
24	39	M	LOA	PR	TMZ	NO	CP+SGTC	LEV 3000 PB 200	150	3	20	27	>50%		No co-operation	NO	NO
25	64	M	GBM	PR	FTMU+Beva-cizumab	YES	SP+SGTC	TPM 200	150	6	2	6	>50%		-	YES	NO

AO: anaplastic oligodendroglioma; AOA: anaplastic oligoastrocytoma; AA: anaplastic astrocytoma; LGA: low-grade astrocytoma; GC: gliomatosis cerebri; GBM: glioblastoma multiforme; MEN: meningioma; MET: brain metastases; LOA: low-grade oligoastrocytoma; GTR: gross total resection; PR: partial resection; TMZ: temozolomide; FTMU: fotemustine; SP: simple partial; CP: complex partial; SGTC: secondary generalised tonic-clonic; CNZ: clobazan; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; PB: phenobarbital; TPM: topiramate; VPA: valproic acid; DP: disease progression; SE: side effects; Efficacy: ≥50% reduction of seizure frequency; W: seizure worsening.

Table 2. Comparison of tests between baseline and last available follow-up visit for each patient in the whole group (*n*=25).

	Baseline	Follow-up	Paired T-test *p* value
KPS	96.8±7.8	96.4±7.9	0.564*
BI	97.5±6.8	96.6±7.8	0.157*
MMSE	28.6±1.9	28.5±1.7	0.888*
QOLIE 31P (V2)			
Seizure worry	47.3±30.7	67.1±21.0	**0.004**
Overall QoL	61.2±18.8	56.1±18.5	0.468
Emotional well-being	61.1±23.3	58.3±18.3	0.789*
Energy/fatigue	55.7±22.8	58.9±18.2	0.711
Cognitive effects	65.2±28.7	68.0±22.3	0.571
Medication effects	45.0±33.3	53.4±24.0	0.374*
Social function	56.7±24.7	69.9±24.1	0.108
Distress related to seizures	2.8±1.5	2.3±1.2	0.339*
Distress related to QoL	2.3±1.3	2.1±1.3	0.510*
Distress related to emotions	2.5±1.1	2.3±1.2	0.459
Distress related to energy	2.4±1.3	1.7±0.7	0.095*
Distress related to cognitive effects	2.7±1.4	2.3±1.2	0.500*
Distress related to drugs	3.3±1.3	1.8±1.0	**0.009***
Distress related to social life	2.8±1.3	1.6±1.0	**0.008***
Health thermometer	58.6±26.3	62.8±19.0	0.642
AEP	40.4±13.4	37.6±9.8	0.356
EORTC QLQ-C30			
Functional scale	66.3±19.2	71.6±15.4	0.220
Symptoms scale	19.3±10.4	18.1±12.6	0.779
QoL	67.2±16.8	68.9±11.1	0.682
Zung Self Depression Rating Scale	31.1±9.6	30.5±7.3	0.745
HAM-A	19.3±6.2	13.7±3.3	**0.002***

* Wilcoxon test.

QOLIE-31-P (p=0.018), a significant decrease in the distress scores related to energy/fatigue, AEDs and social life (p=0.047, p=0.009, and p=0.008, respectively), and a significant decrease in HAM-A score (p=0.017) (*data not shown*).

In patients who had radiological disease progression, we found no significant difference in KPS, BI, MMSE, EORTC-QLQ-C30, AEP, ZSDRS, or QOLIE-31-P and a significant decrease in HAM-A score (p=0.043) (*data not shown*).

In order to assess whether a change in mean SF at baseline could influence results of the QOLIE-31-P test in patients who had stable disease, we performed the Mann-Whitney test between the means of weekly seizures in both groups before treatment. The result was not statistically significant (p=0.931).

Discussion

When taking into consideration both efficacy and pharmacokinetics data, the fact that new AEDs appear to present as a better choice for patients with BTRE has been widely documented in the literature to date (Perry and Sawka, 1996; Striano *et al*., 2002; Newton *et al*., 2005; Maschio *et al*., 2006; Maschio *et al*., 2008; Novy *et al*., 2009; Maschio *et al*., 2009a; Maschio *et al*., 2009b; Maschio *et al*., 2011a; Maschio *et al*., 2011b).

For this reason, we performed a preliminary pilot study to test a new AED, pregabalin, as add-on therapy in patients with BTRE. The main limitation of this present study is the short follow-up period and the limited number of patients, which was further decreased due

to three patients who dropped out as a result of a lack of cooperation. This was because of the distance between our centre and the patients' home and these patients continued their treatment closer to their cities of residence.

We observed a significant effect on seizure freedom and a significant reduction on weekly SF. To date, there has been only one study that evaluated the efficacy of PGB (Novy *et al*., 2009) in the treatment of BTRE. It was a small, retrospective case series (nine patients) that demonstrated good efficacy of PGB both as monotherapy and add-on treatment. In this study, all patients experienced a 50% seizure reduction and 6 patients (66.6%) were seizure-free, with a median duration of follow-up of five months.

In our study, in the ITT population, five patients were seizure-free (41.7%) with a responder rate of 76% and, in patients who completed six months of follow-up, 9 patients were seizure-free (36%) with a responder rate of 91%. Our results demonstrate similar efficacy to that reported by Novy *et al*., however, our population was larger.

In the whole population, we observed 4 patients (16%) with an increase in SF (in 2 patients this was related to disease progression), forcing us to alter the treatment by adding another AED or substituting PGB. These results are similar to those reported in the study of Carreño *et al*. (2007) on refractory partial seizures (15.8% of patients showed inefficacy of PGB).

Concerning the efficacy of other new AEDs as add-on treatment in BTRE, to date, other studies have investigated the effect of lacosamide, levetiracetam and zonisamide. These studies reported a percentage of seizure freedom ranging from 0 to 47.4% (Newton *et al*., 2005; Maschio *et al*., 2006; Maschio *et al*., 2009b; Maschio *et al*., 2011b). The efficacy of PGB observed in our study falls within this range.

Concerning tolerability, in our study, we observed two significant side effects (in 8% of the patients; 1 patient with dizziness and another with irritation and dryness of the eye) and no mild reversible side effects. Concerning the side effects of other new AEDs as add-on treatment in BTRE, to date, other studies have investigated the effect of lacosamide, levetiracetam and zonisamide and reported a percentage of side effects ranging from 0 to 37% (Newton *et al*., 2005; Maschio *et al*., 2006; Maschio *et al*., 2009b; Maschio *et al*., 2011b). Concerning side effects of PGB observed in the literature for both BTRE and non-oncological patients, percentages ranged from 7 to 60%. (French *et al*., 2003; Carreño *et al*., 2007; Novy *et al*., 2009). The small percentage of side effects in our study falls within the range reported in these studies.

Concerning neuropsychological test results, for all patients at the final follow-up visit, we observed an improvement in scores of the anxiety scale. This improvement was maintained even when patients with stable disease and those with disease progression were considered separately. This effect could be due to the direct anxiolitic action of PGB, independent of both the stage of disease and antiepileptic efficacy.

The performance status and global cognitive level assessed using KPS, MMSE, and BI and the perception of quality of life assessed using the EORTC remained unchanged over time. Also, mood remained unchanged and Zung scores remained within the normal range.

Regarding the scale for quality of life in epilepsy (QOLIE 31P), we observed in the whole population a decrease in scores related to "seizure worry" and a decrease in distress related to AEDs, energy/fatigue and social life. This result also remained statistically significant in the subgroup of patients who had stable oncological disease (n=16).

Although the sample size was small, our data still demonstrate a statistically significant effect of PGB on seizure control in patients with stable disease and also an improvement of subscale scores of QoL tests in epilepsy.

Conclusions

This is the first study which evaluates the impact of PGB as add-on treatment on seizure control, QoL, and anxiety in patients with BTRE. Although this is a small series with a relatively short follow-up period (inherent to the survival of patients with brain tumours), our data indicates that PGB might be a new and viable, alternative therapy in this patient population. We hope that there will be future studies on PGB, intent on studying larger groups of BTRE patients with minimum drop-out rate. Given these results, we can hypothesize that for patients with stable oncological disease (receiving no systemic treatment related to brain tumour), epilepsy and its pharmacological treatment seem to be the most important factors that influence the patient's perception of QoL. In patients with disease progression, on the other hand, it appears that their focus on survival overrides any concerns they might have for symptoms of epilepsy.

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