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CLINICAL STUDY

Lacosamide in monotherapy in BTRE (brain tumor-related epilepsy): results from an Italian multicenter retrospective study

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Abstract

Purpose Lacosamide (LCM) is a third-generation anti-seizure medication (ASM) approved for focal onset epilepsy in patients aged ≥ 4.378 Previous studies have reported an efficacy of LCM as add-on treatment in brain tumor-related epilepsy (BTRE). To date, there are no studies in the literature focusing on lacosamide used in monotherapy to treat BTRE. In our retrospective study we investigated efficacy and tolerability of LCM in monotherapy in a multicenter national cohort of primary brain tumor patients.

Methods We collected from 12 Italian Centers 132 patients with primary brain tumors who were treated with LCM in monotherapy. For each patient we evaluated seizure freedom at 3 and 6 months (primary endpoints), side effects and drop-out rate (secondary endpoints).

Results Overall, LCM led to seizure freedom in 64.4% of patients at 3 months and 55% at 6 months. Patients who used two or more ASMs before LCM had a worse seizure control than patients in monotherapy with LCM as first choice.
In 14 patients, we observed seizure control despite tumor progression on magnetic resonance (MRI).
Multivariate analysis showed that gross-total resection at diagnosis was significantly associated with higher seizure freedom rate at 6 months.
Side effects were mainly mild (grade 1–2 according to CTCAE classification) and drop-out rate was low (1.5%). Main side effects were dizziness and somnolence.

Conclusions This is the first study showing a good efficacy and tolerability of LCM when used in monotherapy in BTRE. Further prospective studies are needed to confirm these preliminary data, investigating also quality of life and neurocognitive functions.

Keywords Lacosamide · Primary brain tumor · Epilepsy · Seizure freedom · Side effects

Introduction

Seizures are an important problem among patients with brain tumors, with a frequency ranging from 15 to 95% depending on the histology. Dysembryoplastic neuroepithelial tumors (DNETs) and glioneuronal tumors have the highest prevalence (80–100%), followed by diffuse lower grade gliomas (75%), meningiomas (30–60%), glioblastomas (30–50%), brain metastases (20–35%) and primary CNS lymphomas (10%) [1]. Brain tumor-related epilepsy (BTRE) is often drug-resistant and polytherapy is required, thus impacting negatively quality of life and neurocognitive functions in patients with a prolonged life expectancy [2, 3].

Studies on anti-seizure medications (ASMs) in patients with brain tumors consist of retrospective or relatively small prospective studies, which are heterogeneous in tumor histology, seizure frequency, phase of disease, and concomitant antineoplastic treatment [4].

Due to a lack of well-controlled trials, the final choice of ASMs is often based on the individual physician's judgement. Non-enzyme-inducing ASMs are preferred to minimize the risk of drug interactions between ASMs and antitumor agents (chemotherapies and targeted therapies) [5].

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Lacosamide (LCM) is a third generation antiseizure medication, approved for focal onset epilepsy in patients aged ≥ 4 years, The main mechanism of action is slow inactivation of voltage-gated sodium channels; furthermore, LCM seems to interact with collapsine-response mediator protein 2 (CRMP2), thus enhancing neuronal plasticity [6]. Among pharmacokinetic properties the absence of interactions with drugs metabolized by the hepatic cytochromes represents an advantage when treating patients with brain tumors.

In retrospective and prospective series, LCM showed a high efficacy and tolerability when used as add-on therapy in patients with BTRE, with a seizure reduction ≥ 50% at 6 months ranging from 66 to 86%, and a seizure freedom at 6 months ranging from 31 to 43% [7–11]. Main side effects were dizziness, somnolence, blurred vision and fatigue and were usually mild. Thus, retention rate at 6 months, which was evaluated in a European multicentric prospective study, was very high (86%) [11].

To date, there is a lack of studies in the literature focusing on the use of LCM as monotherapy in BTRE [4].

The purpose of this retrospective multicenter study was to assess efficacy and tolerability of lacosamide monotherapy in patients with primary brain tumor-related epilepsy.

Patients and methods

We collected information of patients from institutional databases. Charts were reviewed, interpreted and coded into study variables based on a newly-developed database that was evaluated and analyzed centrally (F.M. and R.R.).

Inclusion criteria were as follows:

- Histological (according to WHO 2016 classification [12]) or radiological diagnosis of primary brain tumor.
- Seizure description according to the new ILAE classification [13].
- Age ≥ 16 years.
- At least two focal-onset seizures in the disease course, with or without evolution from focal to bilateral tonic–clonic seizures.
- LCM used either as primary or secondary monotherapy after withdrawal of previous ASMs. Among patients of the second group, we further distinguished those who initially used LCM as add-on and then were converted to monotherapy, and those who introduced LCM after interruption of previous ASMs due to side-effects or ineffectiveness.

Exclusion criteria were as follows:

- Patients with only perioperative seizures (seizures occurring within 7 days from the neurosurgical intervention).
- Lacosamide used as add-on therapy.

The main endpoints of the study were efficacy (seizure control), evaluated by seizure freedom at 3 and 6 months from start of LCM in monotherapy, and tolerability (number, type and severity of adverse events according to CTCAE staging version 4.0). The reason for choosing a relatively short follow-up after treatment was mainly due to the presence of a significant number of glioblastoma patients who a relatively short life expectancy. Data about seizures were collected by a seizure diary compiled by each patient, helped by their caregivers when necessary. We also evaluated the drop-out rate (number of patients who withdrew the drug or tapered the dose because of side effects).

Statistical analysis

Patient characteristics were described using percentage frequencies for categorical data, mean values for continuous data.

We selected a priori the following factors as potentially associated with seizure freedom at 3 and 6 months: age (< 50 or ≥ 50), sex, duration of epilepsy from first seizure to LCM start (< 1 or ≥ 1 year), seizure type (focal aware, focal with impaired awareness or focal to bilateral tonic–clonic) and frequency (daily/weekly vs monthly/sporadic), number of ASMs used before LCM (none/1/ ≥ 2), tumor location (temporal/other locations), histology (diffuse lower grade gliomas, glioblastomas, glioneuronal tumors, meningiomas), extent of resection (EOR) (gross-total resection versus subtotal/partial resection), and concomitant antineoplastic treatment (yes/no).

Crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) with p values (with a significance level < 0.05) were estimated using multivariate logistic regression models.

Patients with missing data, lost at follow-up or withdrawing LCM before the completion of 6 months of treatment because of side effects were included in the final analysis.

Results

Baseline characteristics of the study population

Overall, we enrolled from 12 Italian centers 132 patients, treated with LCM in monotherapy from 2004 to 2020.

The median age was 49 (range: 17–79 years). 76 patients were men, and 56 women.

The histological diagnosis was available in 126 patients, while in six patients it was suspected based on MRI, as surgery was unfeasible. 66 patients had a diffuse lower-grade (2–3) glioma: grade 2 and 3 oligodendrogliomas

IDH-mutant 1p19q-codeleted were 15 (11.4%) and 14 (10.6%), grade 2 and 3 astrocytomas *IDH*-mutant were 12 (9.1%) and 9 (6.8%), while grade 2 and 3 astrocytomas *IDH*-wildtype were 9 (6.8%) and 7 (5.3%). 33 (25.0%) patients had a diagnosis of glioblastoma, six (4.5%) had a glioneuronal tumor, three (2.3%) a DNET, two (1.5%) a pilocytic astrocytoma and 16 (12.2%) a meningioma. Among the 126 patients who underwent a surgical intervention, 74 had a gross total resection (GTR) while the remaining 52 a subtotal/partial.

In 53 patients the tumor had a frontal location, in 33 a temporal location, in 20 both frontal and temporal and in the remaining 26 patients occipital or parietal.

Forty-nine patients received LCM as primary monotherapy, while 83 patients received LCM as secondary monotherapy (LCM used after one or more other ASMs), either after interrupting previous ASMs because of side effects or ineffectiveness (43 patients) or after initial add-on (40 patients). The median duration of previous add-on treatment was 9.5 months: 60% of patients became seizure-free with the use of add-on LCM and were converted to monotherapy, while the remaining were converted to monotherapy because of side effects of the concomitant antiepileptic drug. Among patients who received LCM as secondary monotherapy, 56 (42.4%) used one ASM and 27 (20.4%) two or more ASMs. 63 patients received levetiracetam, 11 patients oxcarbazepine, 11 sodium valproate, nine carbamazepine, four phenytoin, four topiramate, three phenobarbital, two lamotrigine, two zonisamide, two perampanel and one brivaracetam.

The starting dose of LCM was 200 mg per day (median value), maximum dose 300 mg per day (median value). The median dose of LinteCM used was 250 mg per day (range 100–500 mg).

The mean duration of epilepsy, from first seizure to lacosamide start, was 21.4 months (range 0–348 months). Seizure frequency at the time of LCM start was daily in 13 patients (9.8%), weekly in 32 (24.2%), monthly in 62 (47%) and sporadic (less than one seizure per month) in 25 (19%).

Seizures were focal aware in 69 patients (52.3%), focal to bilateral tonic–clonic in 35 patients (26.5%), and focal with impaired consciousness in only 28 patients (21.2%).

In 68 (51.5%) patients a concurrent antineoplastic treatment was used either at the time of LCM start or during LCM treatment: radiotherapy in 8 patients, chemotherapy in 19 (temozolomide or procarbazine-lomustine-vincristine/PCV) and chemoradiation in 35 patients. In 6 patients the type of treatment was unknown. Conversely, 48.5% of patients were observed with magnetic resonance (MRI) without any need of an antineoplastic treatment. Most of patients (65.2%) were not on steroids at the time of LCM start (Tables 1, 2).

Table 1 Clinical characteristics of the study population

Variable	No	%
No of patients	132	
Age		
< 50	68	51.5
≥ 50	64	48.5
Sex		
Male	76	57.6
Female	56	42.4
Type of tumor		
Diffuse lower-grade glioma	66	50.0
Glioblastoma	33	25.0
Meningioma	16	12.2
Glioneuronal tumor—DNET	9	6.8
Pilocytic astrocytoma	2	1.5
No histological diagnosis	6	4.5
Tumor location		
Frontal	53	40.2
Temporal	33	25.0
Fronto-temporal	20	15.2
Other	26	19.7
Extent of surgical resection		
Gross total	74	56.1
Subtotal/partial	52	39.4
No surgical intervention	6	4.5
Concomitant antineoplastic treatment		
Yes	68	51.5
No	64	48.5
Type of antineoplastic treatment		
Radiotherapy	8	11.8
Chemotherapy	19	27.9
Chemoradiation	35	51.5
Unknown	6	8.8
Steroids		
Yes	46	34.8
No	86	65.2

Seizure response to lacosamide

Data concerning seizure response at 3 and 6 months were available in 115 patients, while 17 patients were lost at follow-up and two patients withdrew LCM before the completion of 6 months of treatment.

Overall, 64.4% and 55.0% of patients included in the study were seizure-free at 3 and 6 months following LCM in monotherapy.

The seizure freedom rate at 3 and 6 months was 63.3% and 46.9% for patients who received primary LCM monotherapy, 62.8% and 58.1% for those who received LCM monotherapy after interrupting previous ASMs, and 67.5%

Table 2 Seizure characteristics at baseline of the study population

Variable	No	%
Seizure frequency		
Daily	13	9.8
Weekly	32	24.2
Monthly	62	47.0
Sporadic	25	19.0
Seizure type		
Focal aware	69	52.3
Focal with impaired awareness	28	21.2
Focal to bilateral tonic–clonic	35	26.5
Epilepsy duration at lacosamide start (months)		
< 12	86	65.1
≥ 12	46	34.9
Epilepsy duration (months)	21.4 (mean) 4 (median)	
Number of anti-seizure medications used before lacosamide		
0	49	37.1
1	56	42.4
≥ 2	27	20.5

and 62.5% for those who received LCM monotherapy after initial add-on.

In patients who used one ASM before LCM, seizure freedom was 69.6% at 3 months and 67.8% at 6 months, while in patients treated with two or more ASMs before LCM seizure freedom rate was lower (55.6% and 44.4% at 3 and 6 months, respectively). Patients who were treated with two or more ASMs before LCM ($n = 27$) had a significantly younger age (being those < 50-year-old 20/27, 74.1% vs 48/105, 45.7%, $p = 0.009$), a significant prevalence of low-grade gliomas (21/27, 77.8% vs 59/105, 56.2%, $p = 0.041$), a longer history of brain tumor-related epilepsy (> 1-year in 21/27, 77.8% vs 24/105, 22.9%, $p < 0.001$), and were less likely to undergo concomitant antineoplastic treatments (10/27, 37.0% vs 58/102, 56.9%, $p = 0.067$).

Due to the different mechanisms of epileptogenesis, we evaluated seizure control separately across the different histological subtypes: seizure freedom rate at 3 and 6 months was 63.6% and 56.1% in lower-grade gliomas, 66.7% and 54.5% in glioblastomas, 66.7% at both 3 and 6 months in DNETs and glioneuronal tumors, and 68.7% and 62.5% in meningiomas. Among patients without a histological diagnosis, seizure freedom rate was 37.5% and 25.0% at 3 and 6 months respectively.

Patients who were not on steroids had a better seizure control at 6 months than patients taking steroids (seizure freedom rate 61.6% vs 45.5%). Conversely, seizure freedom rate at 3 months was similar in the two groups (66.3% and 63.6%).

The median effective dose of LCM used to obtain seizure control was 250 mg per day.

In 14 patients (16.9% of responders) we observed a seizure freedom following LCM despite tumor progression on MRI: in five patients the progression was documented at 3 months, in eight patients at 6 months and in one patient both at 3 and 6 months.

We did not observe any death.

A multivariate analysis on the whole cohort with histological diagnosis showed that patients who underwent a gross total resection of the tumor derived higher seizure freedom at 6 months following LCM, as compared to patients with subtotal/partial resection ($p = 0.047$), while we did not find any significant correlation between seizure freedom rate at 3 and 6 months and age, sex, number of previous ASMs, epilepsy duration, histology, tumor site, seizure type and frequency, concomitant antineoplastic treatment, and disease progression (Table 3). However, we observed a worse seizure control in patients who used two or more ASMs before LCM but without reaching a statistical significance maybe due to the small sample size.

We also investigated in a multivariate analysis whether the IDH mutation, 1p/19q codeletion and tumor grade had an impact on seizure freedom at 3 and 6 months among patients with lower-grade gliomas: *IDH* mutation, 1p/19q codeletion and the tumor grade did not significantly correlate with seizure control. Conversely, in the same subgroup, the use of steroids significantly correlated with a lower seizure freedom at 6 months (OR 0.05, $p = 0.029$) (Table 4).

Side effects and adherence to treatment

Adverse events during LCM therapy were reported in 13 patients (9.8%), being the most frequent somnolence (six patients) and dizziness (three patients). Side effects were more frequent mild (grade 1–2 according to CTCAE staging), and only in three patients (2.5%) were serious (grade 3–4), consisting in excessive sedation (one patient) and psychiatric condition like depressed mood (two patients, grade 1).

Adverse events led to LCM dose reduction in five patients (mean dose reduction 70 mg, range 50–100 mg) and drug withdrawal in two patients (one patient for dizziness and one because of anxiety and depression).

Discussion

To our knowledge, this is the first study focusing exclusively on the use of LCM in monotherapy in patients with brain tumors and epilepsy.

Seizure freedom at 6 months after LCM monotherapy was higher (55%) [8–11] as compared to values reported for

Table 3 Multivariate analysis of factors associated to seizure freedom at 3 and 6 months in patients with a histological diagnosis i in

	Seizure freedom at 3 months				Seizure freedom at 6 months			
	OR	95% C.I		Sig	OR	95% C.I		Sig
		Lower	Upper			Lower	Upper	
Sex								
Male	1				1			
Female	1.664	0.630	4.401	0.304	1.335	0.497	3.585	0.567
Age								
Age < 50 years	1				1			
Age > /= 50 years	1.081	0.354	3.301	0.891	0.735	0.224	2.411	0.611
History of brain-tumor related epilepsy (BTRE)								
History of BTRE < 1 y	1				1			
History of BTRE > /= 1 y	0.916	0.272	3.079	0.887	1.319	0.360	4.830	0.676
Seizure semiology								
Focal aware seizures	1				1			
Focal aware seizures with impared awareness	0.492	0.156	1.550	0.226	0.787	0.226	2.736	0.706
Bilateral tonic–clonic seizures	1.040	0.323	3.346	0.947	1.055	0.331	3.361	0.927
Diagnosis								
Diffuse lower-grade glioma	1				1			
Glioblastoma	1.561	0.396	6.147	0.524	1.884	0.420	8.456	0.408
Glioneuronal tumor / DNET	0.558	0.098	3.169	0.510	0.462	0.079	2.703	0.392
Meningioma	1.580	0.297	8.410	0.592	0.802	0.167	3.852	0.782
Tumor location								
Other	1				1			
Temporal lobe	2.653	0.946	7.440	0.064	1.254	0.467	3.366	0.653
Extent of resection								
No total	1				1			
Gross total	1.131	0.398	3.215	0.818	2.810	1.013	7.799	0.047
Seizure rate								
Monthly / sporadic	1				1			
Daily / weekly	0.627	0.233	1.690	0.356	0.843	0.306	2.320	0.741
Number of antiseizure medications used before lacosamide								
0	1				1			
1	1.067	0.355	3.211	0.908	0.998	0.323	3.083	0.998
2	0.460	0.106	2.002	0.300	0.250	0.052	1.201	0.083
Concomitant antineoplastic treatment								
No	1				1			
Yes	0.585	0.196	1.743	0.336	0.800	0.233	2.747	0.723
Steroids								
No	1				1			
Yes	0.657	0.226	1.912	0.441	0.419	0.135	1.305	0.133
disease progression (at 3 and 6 months, respectively)								
No	1				1			
Yes	0.481	0.217	0.099	0.365	0.984	0.228	4.242	0.983

LCM in add-on therapy (31–43%) (Table 5). Furthermore, a better seizure control was obtained in patients who started LCM as first or second line treatment. Nevertheless, seizure control was significant also in patients who had two or more ASMs before LCM (seizure freedom rate at 6 months of 44.4%).

When compared to other ASMs used in monotherapy in BTRE, LCM showed a similar efficacy to levetiracetam, perampanel and valproic acid and a higher efficacy than oxcarbazepine and topiramate, with fewer side effects than perampanel and oxcarbazepine [14–25]. A recent multicentric retrospective study did not find any

Table 4 Multivariate analysis of factors associated to seizure freedom at 3 and 6 months in lower-grade gliomas

	Seizure freedom at 3 months				Seizure freedom at 6 months			
	OR	95% C.I		Sig	OR	95% C.I		Sig
		Lower	Upper			Lower	Upper	
Sex								
Male	1				1			
Female	5.574	0.708	43.889	0.103	8.182	0.849	78.885	0.069
Age								
Age < 50 years	1				1			
Age > /= 50 years	1.225	0.211	7.094	0.821	0.374	0.046	3.060	0.359
History of brain-tumor related epilepsy (BTRE)								
History of BTRE < 1 y	1				1			
History of BTRE > /= 1 y	2.217	0.311	15.811	0.427	1.112	0.112	11.025	0.928
Seizure semiology								
Focal aware seizures	1				1			
Focal aware seizures with impared awareness	0.625	0.064	6.088	0.685	0.393	0.038	4.066	0.433
Bilateral tonic–clonic seizures	0.629	0.106	3.715	0.609	0.429	0.057	3.255	0.413
IDH mutation								
Absent	1				1			
Present	1.445	0.135	15.435	0.760	0.512	0.038	6.843	0.613
1p19q codeletion								
Absent	1				1			
Present	0.923	0.146	5.836	0.932	1.768	0.223	14.046	0.590
Grade								
3	1				1			
2	0.976	0.215	4.442	0.975	2.968	0.436	20.207	0.266
Tumor location								
Other	1				1			
Temporal lobe	1.818	0.315	10.510	0.504	0.610	0.095	3.900	0.602
Extent of resection								
No total	1				1			
Gross total	1.862	0.396	8.758	0.431	4.295	0.876	21.051	0.072
Seizure rate								
Monthly / sporadic	1				1			
Daily / weekly	0.342	0.061	1.933	0.225	0.220	0.027	1.769	0.155
Number of antiseizure medications used before lacosamide								
0	1				1			
1	0.431	0.061	3.073	0.401	1.918	0.227	16.221	0.550
> /= 2	0.547	0.046	6.572	0.634	2.375	0.156	36.213	0.534
Concomitant antineoplastic treatment								
No	1				1			
Yes	1.101	0.134	9.058	0.929	1.924	0.186	19.890	0.583
Steroids								
No	1				1			
Yes	0.699	0.106	4.618	0.710	0.051	0.004	0.739	0.029
Disease progression (at 3 and 6 months, respectively)								
No	1				1			
Yes	0.123	0.008	1.816	0.127	0.437	0.011	17.417	0.660

Table 5 Seizure freedom and side effects in studies on LCM in brain tumor-related epilepsy

Study	Type of study	Treatment modality	No of patients	Histology	Seizure freedom at 3 months	Seizure freedom at 6 months (%)	Side effects	Follow-up (months)
Villanueva V, et al. Epilepsy Behav, [8]	Retrospective Multicentric Real-life	Both add-on and monotherapy	105 (102 add-on, 3 monotherapy)	Gliomas (gr 2, 3, 4) Meningiomas Ependymomas Glioneuronal tumors Brain metastases	30.4%	30.8	Somnolence dizziness, fatigue	6
Maschio M, et al. Epilepsy Behav, [9]	Prospective	Add-on	22	Gliomas (gr 2, 3, 4)	–	31.8	Dizziness, blurred vision	6
Rudà R, et al. J Neurooncol. [10]	Prospective	Add-on	71	Gliomas (gr 2, 3, 4)	42.2%	43	Dizziness	9
Rudà R, et al. Epilepsia, [11]	Prospective Multicentric	Add-on	93	Gliomas (gr 1, 2)	–	35	Dizziness, headache, nausea, asthenia	6
Present study	Retrospective and Real-life	Monotherapy	132	Gliomas (gr 1, 2, 3, 4) Meningiomas Glioneuronal tumors	64.4%	55	Somnolence, dizziness, depression	6

statistically significant difference in the cumulative incidence of treatment failure from any reason between LCM and lamotrigine among patients who mainly received the drugs in add-on [14].

Regarding the histological type, we found a similar seizure control in glioblastomas and grade 2–3 gliomas, while in the literature a worse seizure control is described in glioblastomas [26]. We reported also a good seizure control in patients with meningiomas and glioneuronal tumors: the seizure freedom rate at 6 months was 58.8% and 54.5%, respectively. Among lower-grade glioma both *IDH* mutation and tumor grade were not correlated with seizure freedom following LCM.

Our study confirms the positive correlation between extent of resection (EOR) and long-term seizure control [27–32]: patients undergoing gross-total resection reached a condition of seizure freedom more frequently regardless of tumor histology.

This study confirms the good tolerability of lacosamide, and the high adherence to treatment. Similarly to other studies, side effects were reported in a low proportion of patients, and the drop-out rate because of adverse events was low (1.5%).

Conclusions

According to the results of this preliminary study, lacosamide when used in monotherapy is well tolerated and effective in patients with BTRE.

The limits of our study are the retrospective collection of data, implying that possible gaps in information would have occurred, and the lack of information about quality of life and neurocognitive functions during treatment. Furthermore, we investigated seizure control in a heterogeneous study population, including different brain tumor types undergoing different surgical approaches and adjuvant treatments.

Conversely, this is a large national real-life study. Further prospective cohort studies or randomized trials with quality of life and cognitive preservation as secondary end-points are needed in order to better define efficacy and tolerability of lacosamide in monotherapy.

Author contributions FM and RR: designed the study, performed data analysis and wrote the manuscript. SM, VB, SQ, MN, LB., FD, MS, IF, AM, GP, FB, AP, GG, MP, MS, MCN, GLG: contributed to collection of data, interpretation of the results, intellectual contents and

critical revision of the draft AP and FC: contributed to critical revision of the draft.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interests Mo F., Meletti S., Belcastro V., Quadri S., Napolitano M., Bello L., Dainese F., Scarpelli M., Florindo I., Mascia A., Pauletto G., Bruno F., Pellerino A., Giovannini G., Polosa M., Sessa M., Conti Nibali M., Gigli G.L., Pisanello A., Cavallieri F.: did not declare conflicts of interests. Di Gennaro G. joined advisory boards and pharmaceutical industry-sponsored symposia for EISAI, UCB, LivaNova, Arvelle. Rudà R. joined Advisory Boards and received grants from UCB, Mundipharma, Novocure and Bayer.

Consent to participate Informed consent was obtained from all individual participants included in the study.

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