Radiotherapy plus temozolomide or PCV in patients with anaplastic oligodendroglioma 1p19q codeleted

Alberto González-Aguilar, Ignacio Reyes-Moreno, Rosa P. Peiro-Osuna, Alán Hernández-Hernández, Axayacatl Gutiérrez-Aceves, José Santos-Zambrano, Vicente Guerrero-Juárez, Manuel López-Martínez, Elvira Castro-Martínez

Introduction. Radiotherapy with procarbazine, lomustine, and vincristine (PCV) improves overall survival in patients with anaplastic oligodendroglioma 1p19q codeleted.

Patients and methods. This retrospective analysis investigated outcomes in patients with anaplastic oligodendroglioma 1p19q codeleted compared two different protocols (radiotherapy plus temozolomide or PCV). The primary end points were overall survival and progression-free survival. Secondary endpoint was the radiological response.

Results. A total of 48 patients were included. Mean age was 43 years (range: 19-66 years), 26 were male (54.1%). Twenty-one patients received PCV and 27 temozolomide. The baseline characteristics were not difference between the groups. The progression-free survival and overall survival in the PCV group were 7.2 and 10.6 years respectively and temozolomide were 6.1 and 9.2 years, both statistically significant. The radiological response was present in 80.9% in PCV arm and 70.2% in temozolomide arm there was not statistical differences. The multivariate Cox model showed only the significant parameters the use of PCV protocol. The toxicity grade 3 or 4 was present in 42.8% in PCV arm and 11.1% in temozolomide arm.

Conclusions. The most common strategy in the Latin America community is the substitution of the PCV for temozolomide. This retrospective study showed superior efficacy of PCV than temozolomide. The Latin American community effort must be made to be able to have the drugs to available for using as a first line of treatment.

Key words. 1p19q codeletion. Oligodendroglioma. PCV. Temozolomide.

Neurological Center Santa Fe; ABC Medical Center (A. González-Aguilar, I. Reyes-Moreno). Emergency Department (A. González-Aguilar, R.P. Peiro-Osuna, A. Hernández-Hernández, J. Santos-Zambrano, V. Guerrero-Juárez, M. López-Martínez, E. Castro-Martínez); Neurooncology Department (A. González-Aguilar, R.P. Peiro-Osuna, A. Hernández-Hernández); Radioneurosurgery Department (A. Gutiérrez-Aceves); National Institute of Neurology and Neurosurgery Manuel Velasco Suárez; Mexico DF, Mexico.

Corresponding author:
Dr. Alberto González Aguilar. National Institute of Neurology and Neurosurgery Manuel Velasco Suárez. Insurgentes # 3877. Col. La Fama. CP 14269. Mexico DF, Mexico.

E-mail:
albertogonzalez@neurocirugia-innn.com

Accepted:
08.05.18.

How to cite this paper:
González-Aguilar A, Reyes-Moreno I, Peiro-Osuna RP, Hernández-Hernández A, Gutiérrez-Aceves A, Santos-Zambrano J, et al. Radiotherapy plus temozolomide or PCV in patients with anaplastic oligodendroglioma 1p19q codeleted. Rev Neurol 2018; 67: 293-7.

Versión española disponible en www.neurologia.com

© 2018 Revista de Neurología

Introduction

Each year, in the United States, 4,500 to 5,000 patients are newly diagnosed with a grade II or III astrocytoma or oligodendroglioma [1,2]. Typically, patients with low-grade gliomas present between 25 and 45 years of age, whereas patients with anaplastic tumors tend to be slightly older. The brain tumors represent the 2% of all malignant neoplasms. The anaplastic oligodendroglioma (AO) represent only about 5% of primary brain tumors, their management has been the subject of multiple prospective clinical trials [1,2]. The addition of procarbazine, CCNU and vincristine (PCV) chemotherapy, either before or after RT, has been investigated in two large phase III randomized trials (RTOG 9402 and EORTC 26951) [3,4]. Both trials recently underwent updated analyses and for the first time it has been demonstrated in codeleted patients that the addition of chemotherapy to adjuvant radiotherapy is associated with an improved overall survival (OS), thereby establishing the new standard of care for these patients [5]. A current conundrum in the neuro-oncology community is whether temozolomide (TMZ) [6-11] can be substituted for the more toxic PCV treatment [3,4], and no prospective data are available to support this strategy. Lomustina or procarbazine are not available in all Latin America, as result of this, the most common strategy in the Latin America community is the substitution of the PCV for TMZ, although, there is not phase III study that supports this strategy. The purpose of this study is to analyze if the TMZ has the same efficacy of PCV to support the common strategy in populations where these drugs are not available.

Patients and methods

This is a retrospective study, the inclusion criteria were: patients aged ≥ 16 years with oligodendroglioma grade 3 recently diagnosed, Karnofsky Performance Score (KPS) ≥ 70, patients with histological confirmation, patients with the presence of the

Table I. Chemotherapy regimens.

TMZ arm	Temozolomide 75 mg/m^2 orally, daily including weekends during radiotherapy
	150-200 mg/m^2 orally, days 1-5, 4 weeks for six cycles of maintenance treatment
PCV arm	Lomustine: 110 mg/m^2 orally, day 1
	Procarbazine: 60 mg/m^2 orally, days 8-21
	Vincristine: 1.4 mg/m^2 intravenously (max. 2 mg), days 8 and 29, every 6-8 weeks for 6 cycles

1p19q codeletion by FISH, patients treated in National Institute of Neurology and Neurosurgery and treated with radiotherapy plus chemotherapy (TMZ or PCV only) were included.

Fluorescence in situ hybridization (FISH)

Analysis for 1p19q codeletion used for these analyses was performed at Quest diagnostic. We consider as positive codeletion if the mutation is present in 50% of nuclei or more (Research Committee of the European Confederation of Neuropathological Societies criteria) [12].

Neurosurgery and radiological evaluation

Complete resection was considered, such as the removal of the entire macroscopic portion reported by the neurosurgeon and corroborated by neuroimaging. The imaging postoperative was performance in the first 72 hours. The institutional protocol for imaging follow-up is to perform MRI every six months for five years and then once a year. Any neurological deterioration or changes in the patient's clinical condition were indication of new imaging study. We use the Radiological Assessment in Neuro-Oncology (RANO) criteria [11].

Radio and chemotherapy protocol

The institutional treatment is RT given in 1.8 Gy per fraction (to isocenter), one fraction per day, five days per week, to a total of 59.4 Gy in 33 fractions. The chemotherapies protocols are described in table I.

During concurrent radiation TMZ therapy, patients received prophylaxis against *Pneumocystis jirovecii* pneumonia with trimethoprim/sulfamethoxazole, three times per week, or alternatively with either dapsone 50 mg bid (only two protocols available in our country)

Table II. Baseline characteristic by group at onset and statistical differences.

	TMZ arm (n = 27)	PCV arm (n = 21)	p
Mean age	41 years	45.3 years	0.3145
Sex (female/male)	13 / 14	9 / 12	0.7962
KPS	80	85	0.1273
Gross total resection Partial resection Biopsy	13 (48.1%) 12 (44.4%) 2 (7.4%)	12 (52.3%) 8 (38%) 1 (4.7%)	0.7432
Radiological response	19 (70.3%)	17 (80.9%)	0.8319
Progression-free survival	6.1 years	7.2 years	0.0132
Overall survival	9.2 years	10.6 years	0.0036
Toxicity 3-4	3 (11.1%)	9 (42.8%)	0.0016

KPS: Karnofsky Performance Score.

Statistics

Frequency tables with counts and percentages were used to describe pretreatment characteristics, adverse events, and compliance review results. OS and progression-free survival (PFS) were estimated using the Kaplan-Meier method. An OS event was defined as death due to any cause. A PFS event was defined as death due to any cause or radiographic progression (RANO criteria) [11]. OS and PFS were estimated from the date of the biopsy. The log-rank test was used to compare the survival curves of 1p/19q codeleted versus one or neither deleted. The significant result was $p < 0.05$. The results were performance in MedCalc statistical software.

Results

From June 2000 to February 2017, 48 patients were included, mean age was 43 years, 45.8% were women and 54.2% were men. The KPS was in median 80. Patients treated with PCV group were 21 patients and TMZ group were 27 patients. There was no statistical difference in the baseline characteristics between the groups (Table II). The PFS in PCV group was 7.1 years and TMZ group was 6.2 years with significant differences (p = 0.0132; 95% CI: 0.33-0.78) (Fig. 1). The OS in PCV group was 10.6 years

Figure 1. Kaplan Meier curves compared PFS between PCV vs TMZ.

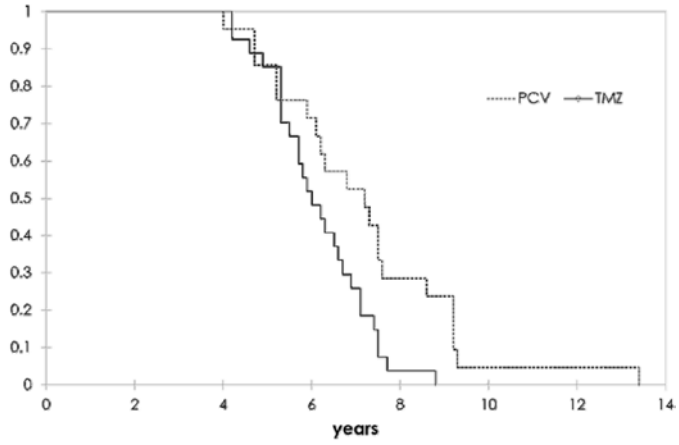
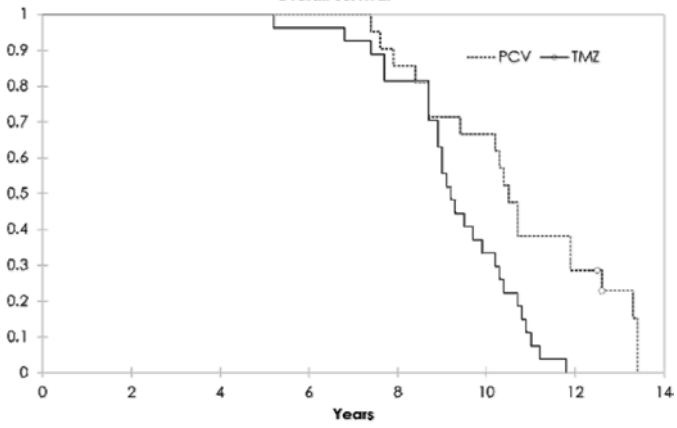
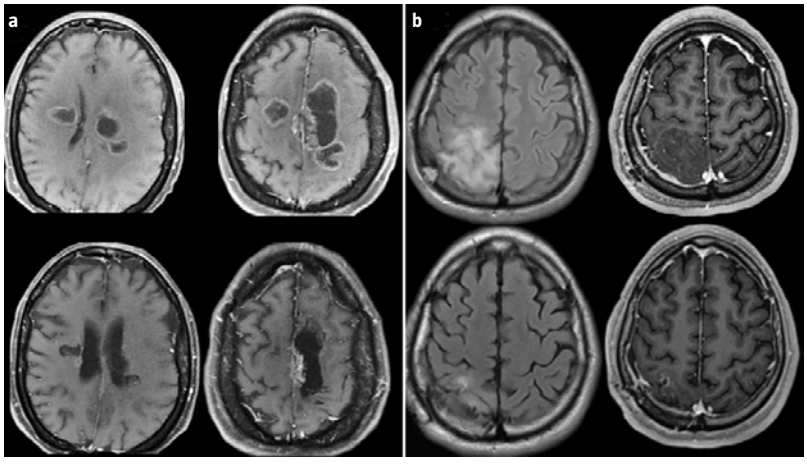


Figure 2. Kaplan Meier curves compared OS between PCV vs TMZ.



and TMZ group was 9.2 years (p = 0.0036; 95% CI: 0.12-0.56) (Fig. 2). We compared the radiological response RR (including partial and complete response) by group with 80.9% in PCV group vs 70.3% in TMZ group (p = 0.8319) (Fig. 3). We compared the toxicity grade 3 or 4 between the groups with a significant difference in PCV group with 42.8% of toxicity vs 11.1% in TMZ group (p = 0.0016). The two principal toxicity were presented, leucopenia and thrombocytopenia. The patients in PCV group only 42.8 % completed the protocol, median 5 cycles (range 3-6); in TMZ group the 80.2% completed the protocol ($p \leq 0.0014$). The Cox multivariate analysis showed only as significant results with the use of PCV protocol with statistical differences in both PFS and OS (Table III).

Figure 3. a) Anaplastic oligodendroglioma radiological response after three cycles of PCV; b) Anaplastic oligodendroglioma radiological response after three cycles of TMZ. Both patients previously received radiotherapy.



Discussion

A current controversy in the neuro-oncology community is whether TMZ can be substituted to PCV because the grade 3 or more toxicity is around 40-60% with PCV [13-15]. In Latin America are not available lomustina neither procarbazine as result of this, the most common conduct in the Latin America community is the substitution of PCV for TMZ but there is not phase III study that supports this change. We analyzed 48 patients, age and sex are very similar to those already described in the two largest series performed by EORTC and RTOG, with the mean age being around 40 years and more frequent in men. Patients treated with PCV group were 21 patients and TMZ group were 27 patients. The PCV was superior in PFS and OS than the TMZ (Figs. 1 and 2). In the two longest series that we mentioned above the survival reported in the patients with the presence of the codeletion 1p19q were as follows. In study RTOG 9402, the PFS was not reached (NR) in the radiotherapy arm plus PCV but with radiation alone was 2.6 years, the OS in radiotherapy plus PCV, NR and the radiotherapy arm alone was 6.6 years. In the EORTC 26951 study,

Table III. Cox multivariate analysis.

	Progression-free survival			Overall survival		
	p	95% CI	HR	*p*	95% CI	HR
Gross total resection	0.3232	0.39-1.35	1.6420	0.6815	0.48-1.59	1.8057
PCV treatment	0.0075	0.19-0.77	0.4925	0.0218	0.24-0.89	0.4439
Radiological response	0.0974	0.26-1.11	1.1491	0.9973	0.50-1.95	1.4289
IDH mutation	0.9423	0.45-2.31	0.9813	0.3361	0.29-1.51	1.4060

the PFS was 13.1 years in patients codeletion and radiotherapy plus PCV, the OS, the result was: not reached vs 9.3 years in arm with radiotherapy alone. The PFS and OS of our study are in accordance to the previously reported with an important benefit of adding chemotherapy in codeleted patients [16]. In the case of series of patients codeleted, treated with TMZ plus radiotherapy compared with radiotherapy plus PCV were not differences in PFS neither OS [17]. We evaluated the RR according to RANO criteria, PCV showed 80.9% CRR vs 70.3% in TMZ group not differences were found it. The CRR were similar and probably the difference with PCV is probably because there is evidence that the PCV protocol may have a longer chemotherapeutic effect [18-20].

We compared the toxicity grade 3 or 4 between the groups finding a significant difference in PCV than the TMZ group. The two principal's toxicities were presented, leucopenia and thrombocytopenia. This toxicity is similar to reported in different clinical trials. Our study shows that the PCV protocol presents much more toxicity than the TMZ but more importantly it improves PFS and OS both statistically significant. In Latin America using TMZ instead of PCV is due to the lack of availability of these drugs but our work shows evidence that PCV treatment is superior in comparison to TMZ, the Latin American scientific community should pressure the regulatory agencies to have access to these chemotherapeutic regimens. We consider that PFS and OS greater than 1 year is a significant value to assume the risk of toxicity of the PCV protocol and to use it. Randomized articles are essential to be able to answer this discrepancy, each patient will have to be analyzed individually and probably in patients with multiple comorbidities the risk exceeds the benefits to choose PCV as first line therapy, but more studies are necessary. The present work shows superiority of PCV vs TMZ. It presents several limitations of being a retrospective study but also allows us to see that a Latin American community effort must be made to be able to have the drugs to give them as a first line of treatment.

References

1. Louis DN, Perry A, Reifenberger G, Von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016; 131: 803-20.
2. Ostrom QT, Gittleman H, Xu J, Kromer C, Wolinsky Y, Kruchko C, et al. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2009-2013. Neuro Oncol 2016; 18 (Suppl 5): S1-75.
3. Intergroup Radiation Therapy Oncology Group Trial 9402. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma. J Clin Oncol 2006; 24: 2707-14.
4. Van den Bent MJ, Carpentier AF, Brandes AA, Sanson M, Taphoorn MJ, Bernsen HJ, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. J Clin Oncol 2006; 24: 2715-22.
5. Kouwenhoven MC, Kros JM, French PJ, Biemond-ter Stege EM, Graveland WJ, Taphoorn MJ, et al. 1p/19q loss within oligodendroglioma is predictive for response to first line temozolomide but not to salvage treatment. Eur J Cancer 2006; 42: 2499-503.
6. Baumert BG, Hegi ME, Van den Bent MJ, Von Deimling A, Gorlia T, Hoang-Xuan K, et al. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. Lancet Oncol 2016; 17: 1521-32.
7. Yung WK, Prados MD, Yaya-Tur R, Rosenfeld SS, Brada M, Friedman HS, et al. Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group. J Clin Oncol 1999; 17: 2762-71.
8. Van den Bent MJ, Taphoorn MJ, Brandes AA, Menten J, Stupp R, Frenay M, et al; European Organization for Research and Treatment of Cancer Brain Tumor Group. Phase II study of first-line chemotherapy with temozolomide in recurrent oligodendroglial tumors: the European Organization for Research and Treatment of Cancer Brain Tumor Group Study 26971. J Clin Oncol 2003; 21: 2525-8.
9. Taal W, Dubbink HJ, Zonnenberg CB, Zonnenberg BA, Postma TJ, Gijtenbeek JM, et al; Dutch Society for Neuro-Oncology. First-line temozolomide chemotherapy in progressive low-grade astrocytomas after radiotherapy: molecular characteristics in relation to response. Neuro Oncol 2011; 13: 235-41.
10. Chang S, Zhang P, Cairncross JG, Gilbert MR, Bahary JP, Dolinskas CA, et al. Phase III randomized study of radiation and temozolomide versus radiation and nitrosourea therapy for anaplastic astrocytoma: results of NRG Oncology RTOG 9813. Neuro Oncol 2017; 19: 252-8.
11. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 2010; 28: 1963-72.
12. Woehrer A, Sander P, Haberler C, Kern S, Maier H, Preusser M, et al; Research Committee of the European Confederation of Neuropathological Societies. FISH-based detection of 1p19q codeletion in oligodendroglial tumors: procedures and protocols for neuropathological practice a publication under the auspices of the Research Committee of the European Confederation of Neuropathological Societies (Euro-CNS). Clin Neuropathol 2011; 30: 47-55.

13. Buckner JC, Shaw EG, Pugh SL, Chakravarti A, Gilbert MR, Barger GR, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. N Engl J Med 2016; 374: 1344-55.
14. Van den Bent MJ, Brandes AA, Taphoorn MJ, Kros JM, Kouwenhoven MC, Delattre JY, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol 2013; 31: 344-50.
15. Cairncross JG, Wang M, Jenkins RB, Shaw EG, Giannini C, Brachman DG, et al. Benefit from procarbazine, lomustine, and vincristine in oligodendroglial tumors is associated with mutation of IDH. J Clin Oncol 2014; 32: 783-90.
16. Wick W, Roth P, Hartmann C, Hau P, Nakamura M, Stockhammer F, et al; Neurooncology Working Group (NOA) of the German Cancer Society. Long-term analysis of the NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with PCV or temozolomide. Neuro Oncol 2016; 18: 1529-37.
17. Lassman AB, Iwamoto FM, Cloughesy TF, Aldape KD, Rivera AL, Eichler AF, et al. International retrospective study of over 1000 adults with anaplastic oligodendroglial tumors. Neuro Oncol 2011; 13: 649-59.
18. Van den Bent MJ, Baumert B, Erridge SC, Vogelbaum MA, Nowak AK, Sanson M, et al. Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study. Lancet 2017; 390: 1645-53.
19. Kaloshi G, Roci E, Rroji A, Ducray F, Petrela M. Kinetic evaluation of low-grade gliomas in adults before and after treatment with CCNU alone. J Neurosurg 2015; 123: 1244-6.
20. Bouffet E, Mornex F, Jouvet A, Thiesse P, Mertens P, Helfre S, et al. Assessment of procarbazine, vincristine and lomustine association (PCV protocol) in oligodendroglioma and mixed glioma. Bull Cancer 1997; 84: 951-6.

Radioterapia más temozolomida o PCV en pacientes con oligodendroglioma anaplásico con codeleción 1p19q

Introducción. La radioterapia con procarbacina, lomustina y vincristina (PCV) mejora la supervivencia global en pacientes con oligodendroglioma anaplásico con codeleción 1p19q, pero no está disponible en América Latina.

Pacientes y métodos. Análisis retrospectivo comparando dos protocolos diferentes, radioterapia más temozolomida o PCV, en pacientes con oligodendroglioma anaplásico con codeleción 1p19q. Los objetivos primarios fueron la supervivencia global y la supervivencia libre de progresión, y el objetivo secundario, la respuesta radiológica.

Resultados. Se incluyó a 48 pacientes, 26 de ellos varones (54,1%), con una edad media de 43 años (rango: 19-66 años). Veintiún pacientes recibieron PCV, y 27, temozolomida. Las características iniciales no tuvieron diferencias entre los grupos. La supervivencia libre de progresión y la supervivencia global en el grupo con PCV fueron de 7,2 y 10,6 años, y en el grupo de temozolomida, de 6,1 y 9,2 años, respectivamente, unos resultados estadísticamente significativos. Hubo respuesta radiológica en el 80,9% en el brazo de PCV y el 70,2% en el brazo de temozolomida. El análisis multivariado de Cox mostró como único parámetro significativo el uso del protocolo PCV. El grado de toxicidad 3-4 estuvo presente en el 42,8% en el brazo de PCV y en el 11,1% en el brazo de temozolomida.

Conclusiones. La estrategia más común en América Latina es la sustitución de PCV por temozolomida. Este estudio retrospectivo mostró una eficacia superior de PCV que de la temozolomida. La diferencia obliga a la comunidad latinoamericana a hacer un esfuerzo colectivo para poder tener acceso a los medicamentos para su uso como primera línea de tratamiento.

Palabras clave. Codeleción 1p19q. Oligodendroglioma. PCV. Temozolomida.