Journal of Neuro-Oncology (2018) 136:533–539
https://doi.org/10.1007/s11060-017-2677-4

CLINICAL STUDY

Long-term impact of temozolomide on 1p/19q-codeleted low-grade glioma growth kinetics

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Received: 3 August 2017 / Accepted: 11 November 2017 / Published online: 15 November 2017

Abstract

Although upfront temozolomide (TMZ) has been widely-used to treat 1p/19q-codeleted diffuse low-grade gliomas (LGG), its long-term impact on the growth kinetics of these tumors has not been determined. Based on serial magnetic resonance images we retrospectively evaluated the evolution of the mean tumor diameter (MTD) in 36 progressive 1p/19q-codeleted LGG treated with upfront TMZ. After TMZ onset, all but two patients (94.4%) presented a progressive MTD decrease that lasted for a median duration of 23 months (range 3–114). In 10 patients (27%) MTD regrowth occurred during TMZ treatment and in 22 patients (66%) after TMZ discontinuation. In these patients, median time to MTD regrowth after TMZ discontinuation was 12 months (range 1–88). The rate of MTD regrowth at 3 and 5 years after TMZ onset was 77 and 94%, respectively. Time to tumor progression (TTP) based on volumetric analysis was shorter than TTP based on Response Assessment in Neuro-Oncology (RANO) bidimensional criteria (23 vs. 35 months, $p = 0.05$) and shorter than time to next oncological treatment (23 vs. 46 months, $p = 0.001$). In 10 patients (27%), absence of volumetric analysis led to continue TMZ for a median of 10 cycles after MTD had started to regrow. Volumetric analysis is important to precisely assess chemotherapy efficacy in 1p/19q-codeleted LGG, identify early tumor progression and avoid futile chemotherapy continuation. In the present series, although some long-lasting volumetric responses were observed, most tumors resumed their growth within 3 years after TMZ onset.

Keywords Oligodendroglioma grade II · Temozolomide · Low-grade glioma · Growth kinetics

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Introduction

In adult diffuse low-grade gliomas (LGG), growth kinetic studies based on the dynamic evaluation of the mean tumor diameter (MTD) have provided important information about the natural history and the impact of treatments in these tumors [1]. In untreated LGG, it has been shown that the mean tumor diameter (MTD) increases continuously and that the velocity of diametric expansion is an independent prognostic marker [2–4]. After surgery, it has been demonstrated that LGG resume their growth at the same rate as before surgery [5]. After treatment with radiotherapy or chemotherapy—with temozolomide (TMZ) or Procarbazine, CCNU and Vincristine (PCV)—growth kinetics studies have shown that most LGG present an initial volume decrease followed by volume increase after a variable period of time [6–10].

In order to defer radiotherapy and its potential neurotoxicity, upfront chemotherapy with TMZ has been widely-used in 1p/19q-codeleted LGG requiring a treatment other than surgery [11, 12]. Although this strategy has recently been shown to be as effective as radiotherapy alone in terms of progression-free survival (PFS) in a phase III trial, the long-term impact of upfront TMZ on 1p/19q-codeleted LGG growth kinetics has not been reported [13]. A previous growth kinetics study showed that the rate of tumor regrowth during upfront TMZ was higher in non 1p/19q-codeleted than in 1p/19q-intact LGG and that when TMZ was discontinued in the absence of tumor progression the majority of LGG resumed their progressive growth within a year [7]. However, due to the limited sample-size and the short follow-up, the association between early tumor regrowth after TMZ discontinuation and 1p/19q co-deletion status could not be determined. Herein, in order to evaluate the long-term impact of TMZ on 1p/19q-codeleted LGG growth kinetics we retrospectively analyzed the evolution of the mean tumor diameter (MTD) in a series of patients treated with upfront TMZ.

Materials and methods

We reviewed a series of patients treated for a 1p/19q-codeleted LGG at the Pierre Wertheimer Neurological Hospital of Lyon or at the Pitié-Salpêtrière Hospital of Paris between 2005 and 2014. The following inclusion criteria were used: histological diagnosis of World Health Organization grade II 1p/19q-codeleted and IDH mutated LGG; age $\geq$ 18 years; Karnofsky performance status $\geq$ 70; measurable disease on magnetic resonance imaging (MRI); evidence of progressive disease, either clinically or radiologically; initial treatment with TMZ without previous specific treatment of the tumor except surgery; no suspicion of anaplastic transformation at chemotherapy onset; and available MRI follow-up until tumor progression or for at least 2 years after TMZ discontinuation. Loss of heterozygosity (LOH) of chromosomes 1p and 19q by codeletion and IDH mutation status were assessed as previously described [14].

TMZ was administered orally from days 1 through 5 at a starting dose of 150–200 mg/m^2, repeated every 28 days after the first daily dose of TMZ. In the absence of unacceptable toxicity (repeated grade IV blood toxicity despite 25% dose reduction) or of disease progression, patients continued to receive TMZ for at least 12 cycles and up to 30 cycles, based on the clinical judgment of the referring physician. Patients left the study upon anaplastic transformation (histologically proved or suspected when rapidly growing foci of enhanced contrast appeared on imaging) or when tumor progression required another treatment.

After TMZ onset, at least 4 consecutive MRIs, performed every 3–6 months until tumor progression, were required to evaluate tumor changes. Before TMZ onset, the spontaneous growth of the tumor was analyzed in a subset of patients who had been initially followed prior to TMZ initiation and in whom at least 2 successive MRIs were available over at least a 3-month period.

When only printed images were available (n = 15), tumor volumes were estimated manually by one investigator (C.I.) using the 3-diameter technique ($V = D_1 \times D_2 \times D_3/2$), as previously described [1]. When DICOM images were available (n = 21) the tumor was segmented. Firstly, individual FLAIR images were converted into NIFTI format using MRIcron software [15]. Then, the tumors margins were outlined by a trained clinician (C.I.), who was blinded to patients' treatment status and individual prognoses. This process resulted in the creation of binary images, a volume of interest (VOI) tumor image (in voxels). These volumes were later automatically converted into mm^3 and adjusted for voxel-size using the Matlab software 8.0.0.783 (R2012b) version. The final volume was obtained in mm^3 and the MTD was achieved using the formula: $MTD = (2 \times V)^{1/3}$ [1]. To estimate the slope of the growth curve of the MTD over time for each patient under each condition (before, during, and after TMZ), we performed linear regressions of the MTD of each patient vs. time. Tumor response to TMZ was evaluated using Response Assessment in Neuro-Oncology (RANO) bidimensional criteria for LGG. Progression was defined by the development of new lesions or increase of enhancement (radiological evidence of malignant transformation) or a 25% increase of the T2 or FLAIR non-enhancing lesion compared with baseline scan or best response after initiation of therapy [16]. Time to tumor progression (TTP) based on MTD analysis was defined as the delay between TMZ onset and the first MRI demonstrating unequivocal MTD regrowth or new contrast-enhancement. TTP based on RANO criteria

was defined as the delay between TMZ onset and the first MRI demonstrating progression based on RANO criteria. Time to next oncological treatment was defined as the delay between TMZ onset and new oncological treatment initiation (surgery, radiotherapy and/or chemotherapy) because of tumor progression. Categorical comparisons were performed using Fisher's exact test and a t-test was used for quantitative variables. The survival time was measured from the date of TMZ onset to the date of last follow-up or death. TTP, time to next oncological treatment and overall survival (OS) was estimated using the Kaplan–Meier method and differences between curves were assessed using the log-rank test.

Results

Thirty-six patients fulfilled the eligibility criteria. Their characteristics are presented in Table 1. The median number of TMZ cycles was 18 (range 2–29 cycles). Dose reduction was necessary in 6 patients (18%) who presented a grade III-IV hematological toxicity. Treatment was discontinued after 2 cycles in one patient who developed pneumocystis pneumonia and after 3 cycles in one patient due to severe asthenia. In the absence of tumor progression, patients did not receive radiotherapy or another oncological treatment after TMZ discontinuation.

Before TMZ initiation, median MTD growth rate was assessable in 20 out of the 25 patients who had been previously followed and was 3.2 mm/year (range 1.28–27.9 mm/year; Fig. 1A). After TMZ onset, the MTD continued to increase in 2 patients but progressively decreased in all of the other patients (n = 34) with a median slope of -5.7 mm/year (range − 14.84 to − 0.85 mm/year) and for a median duration of 23 months (range 3–114). MTD regrowth was observed in 32 out of the 34 patients who presented an initial MTD decrease. In 10 patients, it occurred during TMZ treatment (after a median of 10 cycles) and in 22 patients after TMZ discontinuation (after a median of 18 cycles). In these last patients, the duration of volumetric response after TMZ discontinuation was not associated

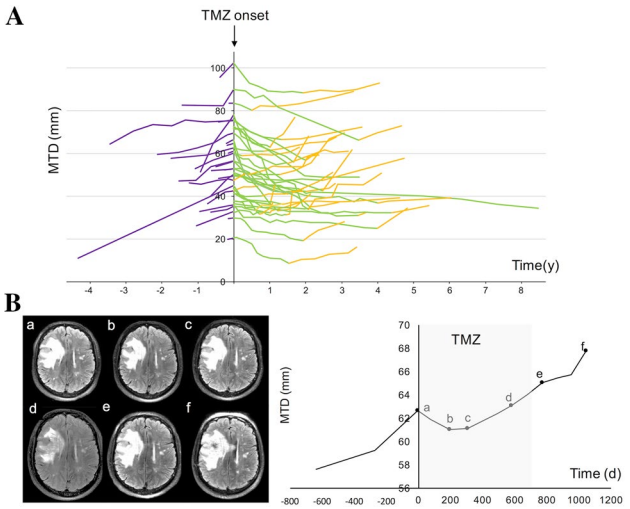

Fig. 1 Evolution of the mean tumor diameter (MTD) before and after temozolomide (TMZ). **A** Evolution of the mean tumor diameter (MTD) before and after temozolomide. For each patient, the evolution of the MTD is shown before (n = 25, violet) and after treatment onset (n = 36): in green during MTD decrease and in yellow after MTD reincrease. **B** Example of a slow tumor regrowth during treatment which, in the absence of volumetric analysis, led to continue TMZ for 12 cycles after the MTD had started to regrow. MTD evolution with corresponding MRI FLAIR images: before TMZ onset (**a**), at the time of maximal response (**b**), at the time of initial MTD regrowth (**c**), during MTD regrowth (**d, e**) and until tumor progression was established by the treating neuro-oncologist (**f**)

Table 1 Patients' characteristics

Variables	N = 36(%)
Gender	
Male	15 (41.7%)
Female	21 (58.3%)
First symptom	
Epilepsy	23 (71.9%)
Other	9 (28.1%)
Type of surgery	
Biopsy	25 (69.4%)
Partial resection	5 (13.9%)
Complete resection	6 (16.7%)
Delay from diagnosis to TMZ onset median (range)	3.35 months (0.13–94.42)
Median age at TMZ onset	45.2 years (26.45–75.59)
Median tumour diameter at TMZ onset	52.76 mm (11.04–102.26)
Karnofsky index at TMZ onset median (range)	90 (70–100)

TMZ temozolomide

with the duration of chemotherapy and median time to MTD regrowth after TMZ disruption was 12 months (range 1–88). In the two patients in whom TMZ was discontinued after only 2 and 3 cycles, the MTD continued to decrease for 19 and 12 months, respectively.

According to RANO criteria, the best response consisted of a partial response in 11 patients (30%), a minor response in 11 patients (30%) and in a stable disease in 14 patients (40%). Median TTP based on MTD analysis was shorter than median TTP based on RANO criteria (23 vs. 35 months, $p = 0.05$) and both TTP based on MTD analysis and on RANO criteria were shorter than median time to next oncological treatment (23 vs. 46 months, $p = 0.001$ and 35 vs. 46 months, $p = 0.08$, Fig. 2). These differences were explained by the fact that at the time of MTD regrowth, most tumors resumed growth slowly, with a growth rate not significantly higher than before TMZ onset (3.2 mm/year vs. 4.62 mm/year, $p = 0.53$) and were therefore initially considered as stable (Fig. 1A, B). Retrospectively, MTD analysis found that in 10 patients (27%), TMZ was continued for a median of 10 cycles after volume had started to regrow.

At progression, next oncological treatment consisted of radiotherapy (n = 12), chemotherapy (PCV n = 8, TMZ rechallenge n = 7, CCNU n = 1, bevacizumab n = 1) and resurgery (n = 3). After a median follow-up of 7 years (range 2.07–11.56), median OS after TMZ onset was 11.5 years. The proportion of patients in whom MTD regrowth was observed was 77, 86 and 94% at 3, 4 and 5 years after TMZ onset, respectively.

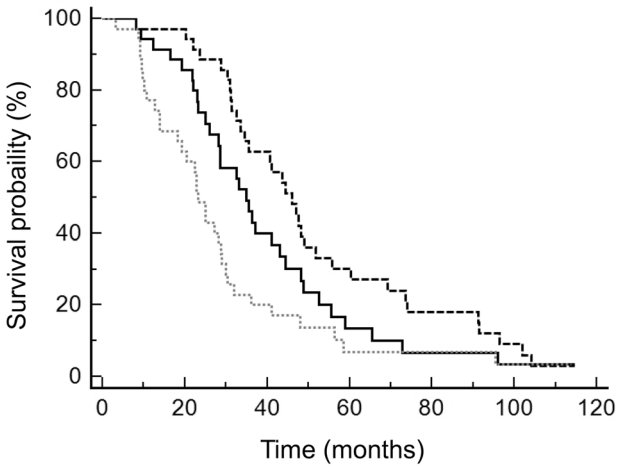

Fig. 2 Time to tumor progression (TTP) and time to next oncological treatment. TTP (in months) according to volumetric analysis (grey dotted line) and to RANO criteria (continuous black line) and time to next oncological treatment (discontinuous black line)

Discussion

In 1p/19q-codeleted diffuse LGG requiring a treatment other than surgery, the optimal therapeutic strategy as well as the most effective way of assessing treatments efficacy remain controversial. In the present study, based on growth kinetics analysis, we observed that nearly all 1p/19q-codeleted LGG treated with upfront TMZ resumed their growth within 5 years after treatment onset. However, their slow growth rate commonly led to overestimate treatment efficacy in the absence of volumetric analysis. These findings suggest that, even in 1p/19q-codeleleted LGG, the most chemosensitive subgroup of LGG, initial treatment with TMZ alone is not sufficient to achieve long-term tumor control. They also show that in these slow growing tumors longitudinal analysis of growth kinetics is particularly important to identify early tumor progression and avoid futile and potentially detrimental chemotherapy continuation.

According to the 2016 WHO classification, three main molecular subgroups of adult LGG can be distinguished. LGG with the 1p/19q co-deletion display the best prognosis, whereas the IDH-mutated gliomas, without 1p/19q co-deletion, have an intermediate prognosis, and the 1p/19q-intact and non-IDH-mutated gliomas have a poor prognosis [17]. Treatment of 1p/19q-codeleted LGG requiring a treatment other than surgery remains debated [18]. On the one hand, the updated results of the RTOG 9802 phase III study demonstrate that in high-risk LGG, radiotherapy plus PCV improves PFS and OS compared to radiotherapy alone [19]. However, owing to their prolonged survival there is a concern that this treatment may result in delayed cognitive dysfunction in patients with 1p/19q-codeleted LGG [20]. On the other hand, the results of the EORTC 22033-26033 phase III study show that, in patients with 1p/19q-codeleted LGG, initial treatment with TMZ has similar efficacy in terms of PFS as initial treatment with radiotherapy alone [13]. Further follow-up is needed to evaluate the impact on cognition and OS, however TMZ may not be the optimal chemotherapy regimen in this setting. In 1p/19q-codeleted anaplastic gliomas, two retrospective studies have reported that upfront PCV resulted in 4–5 years survival advantage in terms of PFS compared to TMZ (7.6 vs. 3.3 years and 9.4 vs. 4.4 years) and there was also trend towards improved OS [21, 22]. In 1p/19q-codeleted LGG, the efficacy of these two chemotherapy regimens has not been compared. However, compared to the reported impact of PCV on 1p/19q-codeleted LGG growth kinetics the present study suggests that, in 1p/19q-codeleted LGG, as in their anaplastic counterpart, upfront TMZ may have a less prolonged effect on volume control than PCV [10, 23]. Indeed, in two studies that

assessed the effect of upfront PCV on 1p/19q-codeleted LGG growth kinetics, no patient was reported to have volume regrowth during treatment, the median duration of ongoing volume decrease after treatment discontinuation ranged between 28 and 35 months and the rates of patients with no volume regrowth at 3 and 5 years after treatment onset were 75 and 60%, respectively [10, 23]. In contrast, in the present study 27% of patients had tumor regrowth during TMZ, the median duration of ongoing volume decrease after treatment discontinuation in the absence of progression was 12 months and the rates of patients with no volume regrowth at 3 and 5 years after TMZ onset were 23 and 6%, respectively.

Mutational analyses in recurrent LGG have demonstrated that TMZ can lead to the acquisition of a hypermutation phenotype that could contribute to malignant progression [24]. It seems therefore particularly important to avoid a potentially detrimental exposure to TMZ in patients who do not benefit from this treatment anymore. However, as observed herein, identification of early tumor regrowth during TMZ can be difficult. In the present study, the 3.8 years median time to next oncological treatment was consistent with the 3.3–4.9 years median PFS reported in previous series of 1p/19q-codeleted LGG treated with upfront TMZ but overestimated the impact of TMZ on LGG volume control [11–13]. It has been well demonstrated that, due to their slow growth rate, untreated LGG are frequently considered as stable although their volume continually grows [3].We observed that the same misanalysis frequently occurred in patients treated with TMZ which could lead to continue this treatment in patients in whom volume has started to regrow. There was an 11 month difference between median time to next oncological treatment and median TTP based on RANO criteria and a 12 month difference between median TTP based on RANO criteria and median TTP based on volumetric analysis. While the first difference illustrates the importance of RANO criteria to monitor LGG patients, the second difference shows that volumetric analysis may provide an earlier identification of tumor progression than RANO criteria. This finding is explained by the fact that according to RANO criteria, tumors that are presenting a slow regrowth will be considered as stable as long as the increase of the area of non-enhancing lesion on T2 or FLAIR MR imaging is below 25% [16]. Conversely, as observed in the present study, many LGG that were initially considered as stable after TMZ onset according to RANO criteria, actually presented a volumetric response. In the future, combining volumetric analysis with longitudinal analysis of 2-hydroxyglutarate using magnetic resonance spectroscopy may further facilitate early response evaluation in IDH-mutant LGG [25].

The optimal duration of TMZ treatment in 1p/19q-codeleted LGG is another unresolved issue [26]. A previous study suggested that a prolonged duration of treatment may be beneficial in continuously responding patients [11]. In the present study, however, we observed at least a 12-month volumetric response in 2 patients who received only 2 and 3 TMZ cycles due to toxicity and we did not find any association between the duration of volumetric response after TMZ discontinuation and the number of cycles received before TMZ discontinuation. In the EORTC 22033-26033 phase 3 study and in a recent phase 2 study, 1p/19q-codeleted LGG patients were treated with a maximum of 12 TMZ cycles which resulted in a and 4.6 and 4.9 years PFS also suggesting that the duration of TMZ treatment may not be a major determinant of the efficacy of this chemotherapy regimen [12, 13].

Other than the limited sample-size and its retrospective design, the present study is limited by the fact that DICOM images were not available in all of the patients and that due to selection criteria regarding available MRI images and follow-up, the present series may not be representative of the population of 1p/19q-codeleted LGG patients. In addition, quality of life, seizure frequency and cognition which in 1p/19q-codeleted LGG may be even more important than volumetric control to evaluate treatment efficacy were not assessed herein [16, 27]. Nevertheless, the present study provides evidence that volumetric analysis is important to precisely assess chemotherapy efficacy in 1p/19q-codeleted LGG and that in these tumors initial treatment with TMZ alone rarely allows long-term volume control.

Funding Cristina Izquierdo was funded by Fundación Alfonso Martin Escudero.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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