Dynamic History of Low-Grade Gliomas before and after Temozolomide Treatment

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Objective: To evaluate the natural progression and the impact of temozolomide in low-grade gliomas and to correlate these changes with the profile of genetic alterations.

Methods: The mean tumor diameter (MTD) of low-grade gliomas was evaluated on serial magnetic resonance images before (n = 39), during, and after (n = 107) treatment with neoadjuvant temozolomide. MTD growth curves were correlated with chromosomes 1p-19q loss and p53 overexpression in the tumors.

Results: Before temozolomide onset, MTD increased linearly over time, indicating a continuous growth that was significantly slower in 1p-19q deleted tumors (3.4 vs 5.9mm/year; $p = 0.0016$) and in tumors that did not overexpress p53 (4.2 vs 6.3mm/year; $p = 0.05$). During temozolomide treatment, almost all patients (92%) experienced initial decrease of MTD. Subsequently, some tumors started to resume growth despite continuous administration of temozolomide, with a lower rate of relapse in 1p-19q deleted tumors (16.6 vs 58%; $p = 0.0004$) and in tumors that did not overexpress p53 (26 vs 68%; $p = 0.003$). When temozolomide was discontinued in the absence of tumor progression, a majority of tumors resumed their progressive growth within a year.

Interpretation: Untreated low-grade gliomas grow continuously at a rate that is influenced by the genetic alterations of the tumors. Temozolomide reverses this pattern at the onset, but this effect is often brief in patients whose tumors overexpress p53 and do not harbor the 1p-19q codeletion, suggesting acquired chemoresistance. A majority of tumors will resume their growth when treatment is discontinued, raising the issue of the optimal duration of treatment in continuously responding patients.

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Detailed kinetic analysis of tumor growth has shown that untreated low-grade gliomas (LGGs) grow continuously and at a relatively predictable rate for many years before malignant transformation.[1,2] Recent studies suggest that chemotherapy may affect this inexorable course because objective responses have been reported in some patients with LGGs, particularly those with chromosome 1p-19q deletions in the tumors.[3–6] These data prompted us to compare the kinetics of LGG growth before and after treatment with temozolomide (TMZ) and to correlate these dynamic changes with the profile of molecular alterations in the tumors.

Patients and Methods

This study analyzed clinical information, collected from patients treated in our department for primary brain tumors, which was entered into a database created in January 1997. The following inclusion criteria were required: histological diagnosis of LGG (oligodendroglioma, oligoastrocytoma, or astrocytoma) World Health Organization grade 2 after central review (M.K., K.M.); age $\geq$ 18 years; Karnofsky performance status $\geq$ 40; measurable disease on magnetic resonance imaging (MRI); evidence of progressive disease, either clinically (progressive neurological deficit that could be ascribed to the tumor or pharmacoresistent epilepsy) or radiologically; and initial treatment with TMZ without previous

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specific treatment of the tumor except surgery. When tumor tissue was available for molecular analysis, informed consent was required.

TMZ was administered orally from days 1 through 5 at a starting dose of 200mg/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 at malignant transformation (histologically proved or suspected when rapidly growing foci of enhanced contrast appeared on imaging) or when tumor progression required a treatment other than TMZ, which was mainly radiotherapy.

Mean Tumor Diameter Estimation and Evaluation of the Mean Tumor Diameter Slope

Before TMZ onset, patients were required to have at least four successive MRIs to be eligible for analysis of the spontaneous growth of the tumor. After TMZ onset, at least four consecutive MRIs were required to evaluate tumor changes, except in patients with progressive disease, in which case progression on two consecutive MRIs after TMZ onset was accepted.

Tumor diameter was determined on joint analysis of sagittal and axial MRI sequences. For each MRI, three diameters were manually measured by two investigators (G. Kaloshi and M-A. Renard) who were blinded to patient treatment status and did not participate in the subsequent analysis of the data. In the axial plane, the largest diameters in the anteroposterior and perpendicular axes were measured on T2-weighted images. In the sagittal plane, only T1-weighted images were available and were used to measure the largest diameter along the vertical axis. The MTD was obtained as the geometric mean of the three diameters, which is the cubed root of their product, as described previously.[1]

To test whether the MTD grew in a linear fashion, as described previously,[1] we performed linear regression of the MTD growth curve with time. However, because patients had various tumor sizes at the time of diagnosis (lead-time bias), which constitute a random variable, a different starting point (intercept) for each patient was allowed and a linear mixed model was used with a random intercept that can be expressed as follows:

$$MTD_{ij} = \mu + \alpha_i + \beta t_{ij} + \varepsilon_{ij}$$

where MTD_{ij} denotes the MTD for Patient i at time of observation j, $\mu + \alpha_i$ is the intercept for the i^{th} patient, β is a fixed effect parameter representing the rate of the MTD growth, t_{ij} is the time of observation j for the i^{th} patient, and ε_{ij} is the residual term for the i^{th} patient at the j^{th} time. To illustrate the differences in MTD growth rate according to molecular status, we plotted each patient's tumor progression curve against the size-adjusted time:

$$t'_{ij} = t_{ij} + \alpha_i/\beta$$

In this way, all of the curves were aligned along common average regression lines according to the slope of their MTD, as demonstrated in Figure 2.

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 MTD of each patient versus time. These slopes of growth of the MTD were then compared between patients of different molecular status.

Evaluation of Maximal Tumor Response

Response determination was estimated from previously reported criteria based on measurable change of the product of the two largest perpendicular diameters of the tumor on axial planes of the MRI (T2 and T1), also taking into consideration the corticosteroid requirement and the results of the neurological examination.[6] Patients still undergoing TMZ treatment at the time of evaluation were included only if they had received at least six cycles of TMZ therapy. Complete response was defined as the complete disappearance of all tumors on T2- or fluid-attenuated inversion recovery–weighted image from the baseline on consecutive MRIs taken at least 8 weeks apart, with the patient not receiving corticosteroids and being neurologically stable or improved (clinical improvement being defined as a $\geq$50% improvement of a neurological deficit or a reduction of at least 75% of the frequency of seizures). Partial response was defined as more than 50% reduction in the size (measured as the product of the largest perpendicular diameters) of the T2- or fluid-attenuated inversion recovery–weighted image maintained for at least 8 weeks together with the use of stable or reduced corticosteroid doses and with the patient being neurologically stable or improved. Minor response was defined as more than 25% to less than 50% reduction in the size (measured as the product of the largest perpendicular diameters) of the T2- or fluid-attenuated inversion recovery–weighted image maintained for at least 8 weeks, with the use of stable or reduced corticosteroid dose and the patient being neurologically stable or improved. Progressive disease was defined as greater than 25% increase in the size of enhancing, nonenhancing tumors or any new tumor on MRI scans, or tumor-related neurological deterioration of the patient while on a stable or increased corticosteroid dose. Stable disease was defined as any other clinical status not meeting the criteria for complete response, partial response, minor response, and progressive disease that was observed for at least 6 months.

Molecular Genetic Methods

Blood and tumor DNA samples isolated according to standard procedures were screened for the loss of heterozygosity on chromosomes 1p and 19q using the following polymorphic markers: D1S468, D1S214, D1S550, D1S2667, D1S234, D1S255, D1S2797, D1S2890, D1S206, D19S219, D19S888, D19S412, and D19S418, as described previously.[6] These microsatellite markers are located in the regions that are commonly lost in oligodendroglial tumors. One of the primers was labeled with Hex, Fam, or Ned fluorochromes (Perkin Elmer, Norwalk, CT). The samples were run on an automatic sequencer and analyzed with

the Gene Scan program (Abi-prism; Perkin Elmer). Tumors were considered as harboring the 1p and 19q deletion when all microsatellite markers for 1p and 19q were lost. In the other cases, including when only 1p or 19q was deleted with the other chromosome intact, the term "no 1p-19q codeletion" was used.

P53 expression was analyzed on 5μm sections of formalin-fixed and paraffin-embedded slides using a monoclonal anti-P53 antibody (1/50, M70001; DakoCytomation, Trappes, France), which was incubated on the slides for 2 hours and visualized by the Envision AP–rabbit–mouse reagent (K4017; DakoCytomation) according to the manufacturer's instructions. Samples were considered positive for p53 expression when more than 10% of the nuclei was labeled.

Statistical Analysis

Nonparametric Wilcoxon tests were performed to compare the mean MTD slopes according to molecular status. Exact χ^2 tests were performed to compare the rates of molecular abnormalities according to evolution modalities. All analyses were performed with SAS software (SAS Institute, Cary, NC).

Results

One hundred and seven patients fulfilled the eligibility criteria, including 39 patients who were also followed before TMZ treatment. Their main clinical, pathological, and molecular characteristics are listed in Table 1.

Chromosome 1p-19q status was evaluated in 68 patients (including 22 patients followed before TMZ treatment) and p53 status in 49 patients (including 22 patients followed before TMZ treatment). Status for both was obtained in 45 patients (including 19 patients followed before TMZ treatment).

As reported previously,[7] the 1p-19q codeletion and p53 overexpression were mutually exclusive ($p = 0.0001$), indicating that these two factors were not independent.

Growth Rates before Temozolomide Onset and Correlation with Molecular Alterations

Thirty-nine patients, whose characteristics are listed in Table 1, had at least four consecutive MRIs with a median follow-up of 3.6 years (range, 1–9.2 years) before the initiation of TMZ. This allowed the analysis of the spontaneous evolution of the MTD (Fig 1). By using a linear regression of diameter versus time for each patient with a mixed model, we observed that the MTD grew in a linear fashion at a rate of 4.76mm/year (95% confidence interval [CI], 4–5.5mm/year). Among patients with known molecular status (see Table 1), the mean MTD growth rate was slower in tumors with 1p-19q codeletion (3.4mm/year; 95% CI, 2.5–4.3mm/year) than in tumors without these alterations (5.9mm/

Table 1. **Patient Characteristics**

Characteristics	Patients Studied after TMZ Onset (n = 107)	Patients Studied before and after TMZ Onset[a] (n = 39)
Median age at first symptoms (range), yr	40 (19-70)	34 (20-57)
Median age at TMZ onset (range), yr	44 (24-72)	39.5 (24-65)
Sex, M/F	62/45	26/13
Histology		
Oligodendroglioma	82	29
Oligoastrocytoma	20	8
Astrocytoma	5	2
Median MTD at TMZ onset (range), mm	50 (18-96)	47 (27-85)
Median duration of follow-up (range), yr	3 (0.5-12.5)	3.6[b] (1-9.2)
Median number of consecutive MRI (range)	11 (2-24)	7[b] (4-17)
Median interval between MRI (range), days	89 (22-416)	199[b] (66-472)
Molecular status		
1p deleted/no 1p deleted	32/36	11/11
19q deleted/no 19q deleted	34/34	9/13
1p-19q codeleted/no 1p-19q codeleted	30/38	9/13
p53 detectable/p53 undetectable	19/30	7/15

[a]These patients are also included in the middle column describing patients studied after temozolomide (TMZ) onset.

[b]Before TMZ onset.

MTD = mean tumor diameter; MRI = magnetic resonance imaging.

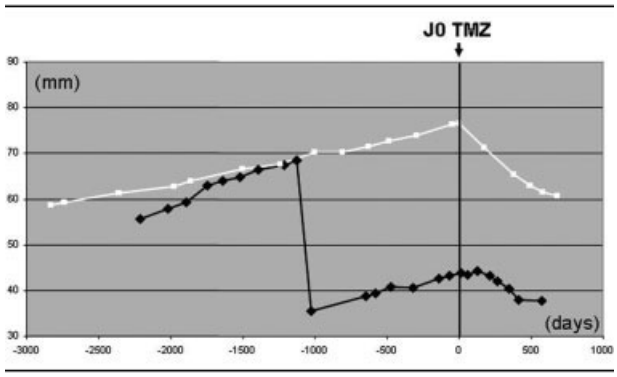

Fig 1. Examples of the evolution of the mean tumor diameter (MTD) over time in two patients before and after temozolomide onset (J0 TMZ). Black line *indicates patient who underwent surgical resection at day −1,000.*

year; 95% CI, 4.5–7.3mm/year; $p = 0.0016$) (Fig 2). Correlations between MTD growth rate and other molecular characteristics are shown in Table 2. Although the 1p-19q deletion was preferentially associated with an oligodendroglial phenotype ($p = 0.012$) and positive p53 expression with an astrocytic phenotype ($p = 0.064$), there was no significant correlation between the MTD growth rate and the tumor histology. This finding is probably related to the low incidence of astrocytic tumors in this cohort, reflecting the "err on the side of the oligodendroglioma" trend in neuropathology.

Evaluation of Tolerance and Maximal Tumor Response after Temozolomide Onset

After a median follow-up of 2 years (range, 0.5–6 years) after TMZ onset, all 107 patients could be evaluated for their response. The median number of TMZ cycles was 17 (range, 2–30 cycles). The treatment was well tolerated, with hematological toxicity as the main side effect. Twelve patients (12%) developed a grade 3 (three neutropenia, three thrombocythemia) or grade 4 (three neutropenia, three thrombocythemia) toxicity. The treatment always could be pursued with dose reduction.

At the time of analysis, 20 patients (18.6%) achieved a partial response, 45 patients (42%) achieved a minor response, 35 patients (32.7%) were stable, and 7 patients (6.5%) had progressive disease. Clinical improvement was observed in 68 (63.5%) patients, whereas 34 (31.8%) patients were clinically stable and deterioration of their condition occurred in 5 (4.7%) patients. Among patients with known molecular status (see Table 1), analysis of the response rate according to the profile of genetic alterations in the tumor is shown in Table 3. Patients with 1p-19q codeletion had a significantly greater rate of objective response as compared with patients who did not harbor the combined deletion (73 vs 50%; $p = 0.03$). No correlation was found between maximal tumor response rates and tumor histology.

Impact of Temozolomide on Mean Tumor Diameter Slopes during and after Temozolomide Treatment

The evolution of the MTD over time for each patient could be followed by curves such as those presented in Figures 1 and 3. Among the 107 included patients, 98 (92%) displayed at least a transient decrease of the MTD curve after TMZ onset (confirmed by at least 4 consecutive MRI evaluations of the MTD). This negative slope corresponded to a breakdown of the MTD growth curve in 38 of 39 patients who had pre-TMZ evaluation of spontaneous tumor growth.

Decrease of MTD occurred immediately after TMZ onset in 77 patients, although this finding was delayed by a median of 116 days (range, 48–206 days) in 21 patients (21%). The groups did not differ by age, molecular data, and tumor size at the onset of TMZ treatment.

In the 98 patients whose MTD decreased initially,

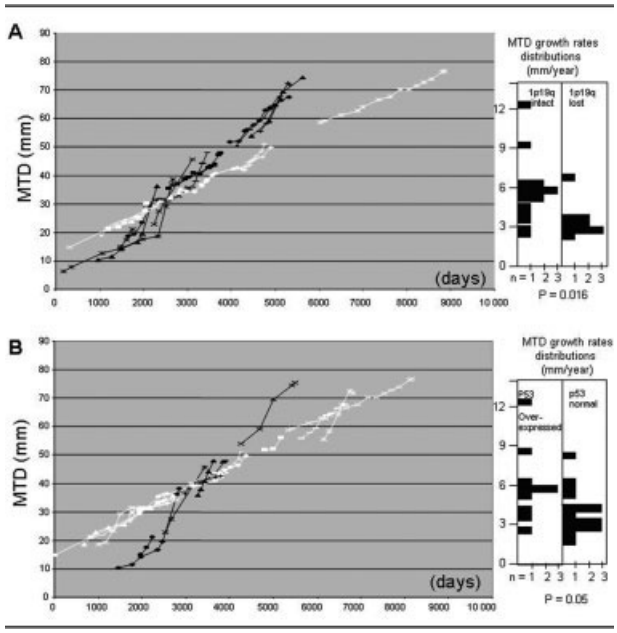

Fig 2. Mean tumor diameter (MTD) evolution after time adjustment before temozolomide (TMZ) treatment. For each patient, the MTD is plotted against its size-adjusted time. (A) Patients without 1p-19q codeleted tumors are plotted in black, and patients with codeleted 1p-19q tumors are plotted in white. (B) Patients with p53 overexpression are plotted in black, and patients with undetectable levels of p53 are plotted in white. By eliminating the lead-time bias, this procedure demonstrates that the spontaneous evolution of the MTD is influenced by the tumor molecular status as 1p-19q deleted tumors display a growth rate of 3.4 versus 5.9mm/year (p = 0.0016) and tumors that overexpress p53 display a growth rate of 6.3 versus 4.2mm/year (p = 0.05). Histograms show the MTD growth rate distributions under each condition.

Table 2. **Mean Tumor Diameter Growth Rate before Temozolomide Treatment according to Molecular Status**

Tumor Characteristics	n	MTD Growth Rate (mm/year)	*p*
1p-19q codeleted/no 1p-19q codeleted	9/13	3.4/5.9	0.0016
1p deleted/no 1p deleted	11/11	4.2/5.6	0.013
19q deleted/no 19q deleted	9/13	3.4/5.9	0.0016
p53 overexpressed/p53 not overexpressed	7/15	6.3/4.2	0.05

MTD = mean tumor diameter.

the average slope of the MTD decrease was −9.2mm/year (95% CI, −8 to −10.5; range, −0.5 to −39.1mm/year). There was no correlation between the slope of decreasing MTD and the age, histology, tumor size at TMZ onset, growth rate before TMZ, or molecular status of the tumors.

However, concurrent with TMZ treatment, 36 of 98 patients (36%) with initial MTD decrease displayed a tumor regrowth characterized by a positive slope of the MTD after a median period of 367 days (95% CI, 290–403; range, 98–756 days). The risk for regrowth while taking TMZ was significantly greater in patients without 1p-19q codeletion (60.6 vs 16.6%; $p = 0.0004$) or when p53 was detectable (70.5 vs 25%; $p = 0.002$).

In 25 patients, TMZ was discontinued not because of tumor progression but because the referring physician believed, on clinical judgment, that the patients had received an appropriate duration of treatment (12 cycles in 7 cases, 18 cycles in 11 cases, 22 cycles in 1 case, 24 cycles in 5 cases, 30 cycles in 1 case) (Fig 4). In these patients, the MTD was evaluated during a median follow-up of 434 days after TMZ discontinuation (range, 84–1,304 days). After discontinuation of TMZ, tumors immediately began growing again in 3 patients, whereas the MTD kept decreasing in 22 patients. However, this decrease was transient as 12 patients displayed regrowth of the MTD after a median delay of 286 days (95% CI, 246–479 days) after TMZ discontinuation.

Discussion

This study emphasizes the interest of dynamic analysis of LGG growth to evaluate the natural progression, as well as the impact of chemotherapy, and to correlate these changes with the profile of genetic alterations in the tumors.

Our data confirm the previous finding that untreated LGGs grow continuously and at a relatively predictable rate during their premalignant phase[1] even if they often appear "stable" on crude visual analysis. The 4.7mm/year spontaneous growth of the MTD found here is quite similar to the 4.1mm/year previously reported,[1] indicating that changes of the MTD over time appear to constitute a reliable marker of the growth of LGG despite the limitations of manual measurements.

The most frequent genetic alterations found in LGG are the codeletion of chromosome 1p-19q, which is preferentially associated with an oligodendroglial phenotype, as well as *TP53* mutations, which are closely linked to p53 expression and preferentially associated with an astrocytic phenotype. In a previous study, we found that chromosome 1p ±19q loss was a favorable prognostic marker for progression-free survival in LGG,[7] but it remains unclear whether this finding is due to a slower spontaneous course or a greater rate of response to treatment, or both. Our present data demonstrating a slower spontaneous growth of the MTD in 1p-19q codeleted tumors (3.4 compared with 5.9mm/year in non–1p-19q codeleted tumors; $p =$

Table 3. **Response Rate to Temozolomide according to Molecular Status**

Molecular Status	No. of Patients	Radiological Response				Clinical Response		
		PR (%)	MR (%)	S (%)	PD (%)	Improve (%)	S (%)	PD (%)
1p-19q codeleted	30	20	53.3	26.7	0	70	30	0
No 1p-19q codeleted	38	15.8	34.2	39.5	10.5	47	45	8
p53 overexpressed	19	15.8	37	42	5.2	58	37	5
p53 not overexpressed	30	30	36.7	26.7	6.6	60	33	7

PR = partial response; MR = minor response; S = stable; PD = progressive disease.

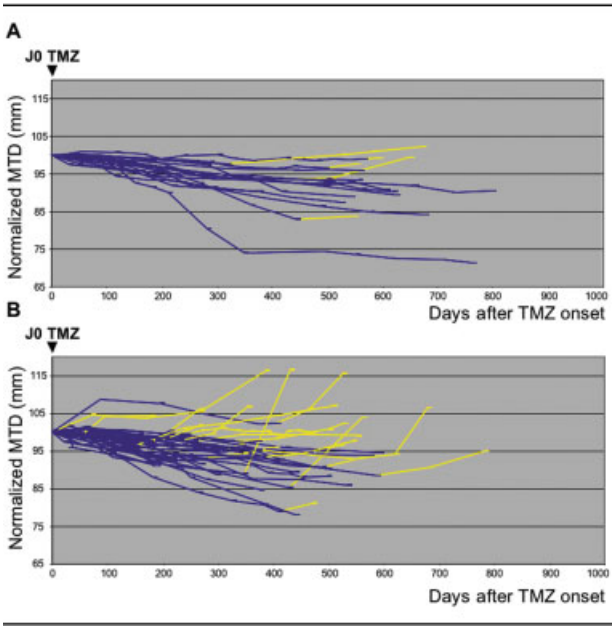

Fig 3. Evolution of the normalized mean tumor diameter (MTD) over time during temozolomide treatment (from J0 TMZ to TMZ discontinuation). For each patient, normalized MTD = 100 + (MTD-MTD at J0 TMZ), and the decreasing part of the curve is plotted in blue and the increasing part is plotted in yellow. (A) Patients with 1p-19q codeletion (n = 30) and (B) patients without 1p-19q codeletion (n = 38). Almost all patients display an initial decrease of the MTD at the onset of TMZ with an average decreasing rate of −9.2mm/year regardless of the 1p-19q status. Relapse occurs more frequently and earlier in tumors without 1p-19q codeletion.

0.0016) suggest a link between 1p-19q codeletion and a slower natural progression of the disease. Conversely, tumors overexpressing p53, an alteration mutually exclusive from 1p-19q deletions,[7–9] had a faster spontaneous MTD growth rate than p53-negative tumors (6.3 vs 4.2mm/year; $p = 0.05$).

The next goal of this study was to evaluate the impact of treatment with TMZ on the dynamic growth curves of the MTD. It is well recognized that some patients with LGG may respond to chemotherapy,[3–6] but evaluation of the response is often hampered by a long delay (up to 1 year or more) before the changes of the tumor become clearly visible on MRI and by the lack of established criteria to measure objective radiological changes.

Using previously reported "static" criteria[3] that simply evaluate maximal tumor response, we found here that 60.6% of patients (65/107) achieved a minor or partial response, whereas 39.4% (42/107) were stable or had progressive disease. However, dynamic analysis of the MTD changes over time showed a more complex and subtle pattern. At the onset of TMZ treatment, the MTD decreased in 92% (98/107) of patients, most often immediately but sometimes after a brief delay, indicating that most tumors display early initial chemosensitivity. This feature is well illustrated in the patients who had both prechemotherapy and postchemotherapy evaluation of the MTD slope, because 38 of 39 experienced a breakdown of the MTD growth curves after chemotherapy onset. During this early stage, the MTD decreased in a linear fashion and a reversal of the mean MTD growth rate corresponded grossly to twice the prechemotherapy MTD growth rate (−9.2 vs +4.7mm/year), albeit with a greater heterogeneity. The slope of the initial MTD reduction was not influenced by the age of patients, histology, tumor size, or type of genetic alterations.

However, after the initial phase of MTD decrease and despite continuous administration of TMZ, the tumors of some patients started to resume growth again whereas others continued to decrease. At this stage, a key difference between 1p-19q codeleted and non–1p-19q codeleted tumors was the frequency of tumor regrowth (see Fig 3). Indeed, tumor regrowth occurred in 16.6% (5/30) of 1p-19q codeleted tumors as compared with 60, 6% (20/33) in non–1p-19q codeleted tumors ($p = 0.0004$). Conversely, tumors overexpressing p53 had a much greater rate of relapse (70.5%, 12/17) than tumors that did not express p53 (25%, 7/28; $p = 0.0027$). Thus, although most tumors displayed an initial chemosensitivity illustrated by a decrease of the MTD at the onset, this effect did not last long enough in tumors without 1p-19q codeletion or in tumors with p53 overexpression to reach the criteria for objective response according to "standard" criteria.

Taken together, these data suggest that acquired chemoresistance is a factor of chemotherapy failure in LGGs. Acquired resistance appears to develop much more frequently and more rapidly in tumors that over-

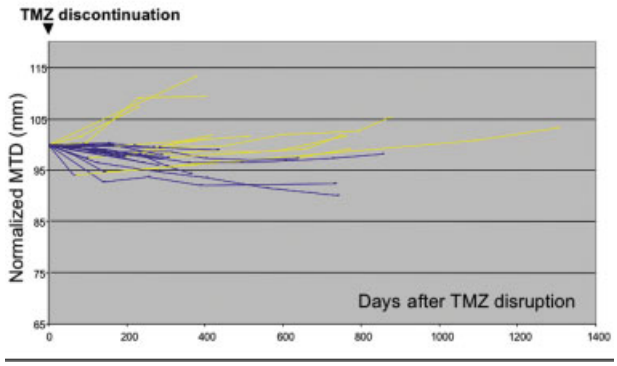

Fig 4. Evolution of the normalized mean tumor diameter (MTD) over time after arbitrary discontinuation of temozolomide. For each patient, normalized MTD = 100 + (MTD-MTD at TMZ discontinuation), and the decreasing part of the curve is plotted in blue and the section representing regrowth is plotted in yellow.

express p53 and do not harbor the 1p-19q codeletion. Genetic instability associated with *TP53* mutations[10] could play a role in the rapid acquisition of a resistant phenotype in this subgroup.

The evolution of the MTD when TMZ was discontinued in the absence of tumor progression is interesting to consider. Because the optimal duration of treatment is unknown, most authors arbitrarily interrupt the treatment after a 12- to 24-month period in nonprogressing patients and pursue a regular follow-up, as we did here. In this setting, a few tumors resume their growth at the first follow-up MRI performed 60 days after TMZ discontinuation, whereas a majority of them remain stable or sometimes continue to decrease despite the interruption of treatment. Nevertheless, a majority of tumors eventually start to grow again, as shown by a 59% rate of MTD regrowth after a median follow-up of 200 days after TMZ discontinuation (range, 60–630 days). This observation raises the question of the validity of an arbitrary interruption of treatment in patients whose MTD is still decreasing when the a priori fixed number of chemotherapy courses has been reached. Should treatment be pursued as long as the MTD continues to decrease, knowing that this option should be balanced with the potential long-term toxicity of prolonged treatment? Alternatively, should we abbreviate chemotherapy to four to six cycles to prevent formation of drug resistance? One could resume chemotherapy once the growth curve points up again.

In summary, dynamic evaluation of MTD changes over time provides relevant information to assess the natural history of LGG, the response to treatment, and the relations between these factors and the genetic alterations in the tumors. This strategy appears useful to identify in-depth changes long before they become detectable by classic visual analysis.

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