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Optimal duration of adjuvant temozolomide in glioblastoma: An unsolved and unsolvable problem

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The standard treatment of glioblastoma with temozolomide concomitant with irradiation and followed by six cycles of adjuvant temozolomide, as initially described by Stupp et al, has not been replaced by any other treatment in more than 15 years, although it has been adjusted according to various patient characteristics, such as age or O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation status.[1,2] Median survival remains, however, clearly unsatisfactory.

Other treatment regimens have failed to improve outcomes, and some modifications of the standard temozolomide treatment have been investigated. A large phase III study compared standard doses of temozolomide with dose-dense schedules with the aim of reducing the levels of MGMT, the main repair protein of temozolomide DNA damage, and thus diminishing its activity. However, no advantage in progression-free survival (PFS) or overall survival (OS) was observed.[3] Another modification involves prolonging the number of cycles of adjuvant temozolomide to 12 or more, with the aim of increasing the PFS and OS of patients whose disease was controlled by the initial treatment. This approach is feasible due to the mild toxicity profile of temozolomide, as well as to its oral administration, which allows a continued administration without major patient discomfort or side effects, although it does involve a not inconsequential economic impact. This extension of adjuvant temozolomide has been used in several clinical trials and has also been implemented in clinical practice despite a lack of clear indications of survival benefits. This extended use of adjuvant temozolomide is based not only on its high tolerability but also on the lack of effective rescue treatments and the somewhat arbitrary nature of using only six cycles in the initial study design.

Nevertheless, several investigators have questioned whether continuing temozolomide beyond six cycles offers any improvement in patient outcome. To provide a reliable answer to this question, it would be necessary to design a randomized study large enough to take into account prognostic factors, such as *MGMT* methylation, the presence or absence of measurable disease, and IDH mutation status. As it is estimated that only 35% of patients initiating treatment can complete the six cycles without experiencing disease progression,[4] in order to have the necessary statistical power, more than 2000 patients would have to be included in the study to reach a sufficient number of patients able to continue treatment with temozolomide for more than six cycles. Since such a trial is not feasible, we must look at the best evidence we have so far.

Results from two retrospective large cohort studies suggest that there might be an increase in PFS in patients who continued temozolomide after the six cycles, but with no effect on OS.[5,6] A randomized but underpowered study by the GEINO group randomized patients at the end of the first six cycles of adjuvant temozolomide and stratified them according to MGMT methylation status and the presence/absence of measurable disease at the time of randomization. Results showed no significant differences in either PFS or OS between patients receiving only six or more than six cycles of temozolomide; these findings held true for patients in all the stratification groups.[7] In contrast, a previous meta-analysis including both prospective and retrospective studies showed an increase in both PFS and OS for patients that continued temozolomide beyond six cycles.[8] However, the diversity of criteria of the trials included in the meta-analysis affects the value of these results. Moreover, the results of the original trials may themselves have been subject to bias, as it can be argued that only patients who survived longer without progression were likely to receive more cycles of temozolomide, while those who progressed or suffered toxicity stopped treatment at six or fewer cycles.

The recent meta-analysis performed by Gupta et al[9] overcame these drawbacks because after an extensive selection of publications, they eliminated all non-randomized, non-comparative, or unpublished reports and limited their study to four randomized trials with quantitative data. Randomization in the individual studies was done either upfront before starting the concurrent phase of temozolomide plus irradiation, after completion of the

concurrent phase and before starting the adjuvant phase of temozolomide, or after completion of the standard six cycles of adjuvant temozolomide. The authors applied an exquisite methodology in accordance with Cochrane methodology and included the Cochrane Risk of Bias tool, the PRISMA guidelines, and the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework, which considers the quality of methodology, directness of evidence, heterogeneity, precision of effect estimates, and publication bias. The pooled analysis of 358 patients showed that continued treatment with temozolomide was not associated with a reduced risk of progression (HR = 0.82, 95% CI: 0.61-1.10; P = .18) or death (HR = 0.87, 95% CI: 0.60-1.27; P = .48) compared to the standard six cycles of adjuvant temozolomide, with no significant difference in toxicity. Nevertheless, when applying the quality of evidence assessment on the benefits or harms of extended vs standard treatment, the quality of evidence for the conclusion remains low.

In summary, after two large cohort studies,[5,6] two meta-analyses,[8,9] and the GEINO randomized trial,[7] it seems that we must accept that extending temozolomide treatment further than six cycles does not confer any clear survival benefit to glioblastoma patients. Despite a wide interest in this question, no one has been or will be able to conduct a sufficiently powered randomized phase III study to answer it, due to both the large number of patients needed and the difficulty of finding funding to carry out a trial of these characteristics. As a consolation, we must consider that even if there were a benefit from prolonging adjuvant temozolomide treatment, this benefit would only be for a relatively small number of patients and the difference between stopping treatment or continuing it would be very small indeed.[10] In my opinion, we have reached our limit in exploiting the possibilities offered by temozolomide and rather than continuing to debate the question of 6 vs 12 cycles of adjuvant treatment, we should dedicate our efforts to the development of new drugs, whatever their mechanism of action, to try to improve the prognosis of this infamous disease.

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