Dose diversification in newly diagnosed glioblastoma

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Unfortunately, there are limited chemotherapy options for newly diagnosed glioblastoma (nGBM) patients, and temozolomide remains the mainstay of chemotherapy treatment. Given its low toxicity profile, a variety of studies evaluating alternative dose schedules to intensify the temozolomide dose have been conducted in order to overcome resistance and improve outcomes.^{1,2} Unfortunately, these studies have failed to show significant benefit with intensification. More recently, some clinical trials even drop the temozolomide in unmethylated O⁶-methylguanine-DNA methyltransferase (MGMT) GBM patients in favor of a novel drug based on a subset analysis suggesting limited benefit of temozolomide in this population of nGBM patients.³ There is even concern that temozolomide may lead to a hypermutated tumor phenotype and more aggressive disease, so who should receive temozolomide and how to optimize its use remains an important clinical question.⁴

Recently, Herrlinger et al published the results of a randomized, phase III trial in nGBM patients with MGMT promoter methylation where the strategy was chemotherapy dose diversification rather than dose intensification.⁵ Based on promising results from the UKT03 trial, patients with nGBM were randomized to standard radiation/temozolomide (Stupp regimen, $N = 69$) or radiation with lomustine given on day 1 and temozolomide on days 2–6 of every 6-week cycle for 6 cycles ($N = 72$). In the modified intention to treat (ITT) analysis, there was a significant improvement in overall survival for the lomustine/temozolomide group (48.1 mo vs 31.4 mo, $P = 0.0492$) which was confirmed in the ITT population (46.9 mo vs 30.4 mo). There was no significant difference in progression-free survival between the 2 groups, which the authors hypothesized was due to an increase in pseudoprogression in the lomustine/temozolomide group. Although patient numbers were small, there were more biopsy-proven pseudoprogression cases in the lomustine/temozolomide group than in the temozolomide group. A post hoc analysis removing the isocitrate dehydrogenase mutant tumors did not substantially alter the results. Toxicity

was modestly increased with the combination of lomustine and temozolomide and fewer patients completed all planned cycles of chemotherapy.

Overall, these results are promising for MGMT-methylated nGBM patients. Both alkylating agents (temozolomide and lomustine) interfere with different cellular replication pathways, highlighting that a multipronged attack blocking multiple pathways may be the most efficacious in patients. However, correct patient selection is critical to the success of combining different chemotherapies. In this study, the authors focused on the MGMT-methylated population, in whom benefit from chemotherapy was anticipated to be greatest and more likely to mirror results in other chemosensitive diseases such as oligodendrogliomas, where radiation with procarbazine, lomustine, and vincristine showed improved survival or in primary CNS lymphoma, where multi-agent chemotherapy serves as the backbone of treatment.⁶ In this era of molecular medicine, the focus has been on tailoring treatment with targeted therapy (eg, targeting epidermal growth factor receptor) but these efforts have not always been successful in GBM, or the duration of response is limited.⁷ Given the heterogeneity of GBM and the Darwinian pressure that single agents exert, dose diversification may be more beneficial than single agent dose intensification if toxicity can be minimized. However, it remains to be seen if dose diversification will benefit other GBM subtypes such as the MGMT-unmethylated population, in whom the response to chemotherapy may be different—again, highlighting the need to have appropriate patient selection.

There were some limitations to this study, including the small sample size. In addition, because of the different administration schedules of the drugs, patients and physicians were not blinded to treatment. Toxicity was increased, raising concerns about expanding this regimen to an older or more debilitated, nonclinical trial population. Regardless of these limitations, the successful completion of a study using 2 known drugs that have been around for many years and the

demonstration of improvement in survival provides hope that we may have the tools at hand to help at least a subset of nGBM patients.

References

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