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Newly diagnosed glioblastoma in the elderly: when is temozolomide alone enough?

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For 40 years, radiotherapy (RT) has been the backbone of treatment for newly diagnosed glioblastoma (GBM).[1] The landmark European Organisation for Research and Treatment of Cancer (EORTC) 26981–National Cancer Institute of Canada (NCIC) trial CE.3 ("Stupp") trial demonstrated that adding alkylator chemotherapy with temozolomide to RT also prolongs survival.[2,3] However, the optimal treatment (as well as definition) of "elderly" patients remains unsettled: patients over age 70 were excluded, and the relative benefit of temozolomide added to RT was reduced with age.[2]The Canadian ClinicalTrials Group (CCTG) CE.6/EORTC 26062 trial was specific to patients ≥65 years, and demonstrated that adding temozolomide to a hypofractionated course of RT also improved survival relative to hypofractionated RT alone.[3] Beyond shortening the course of RT, however, there remains interest in treatment de-intensification among older patients, and neither the EORTC-NCIC nor the CCTG-EORTC trial addressed whether RT could be deferred altogether. A desire to avoid aggressive treatment, particularly RT, may be driven in part by nihilism among patients, families, and providers, but also by the recognition that the elderly experience more toxicity[4] and less relative benefit[2] from aggressive therapy than younger patients. Moreover, the median age at diagnosis of GBM is 65 years,[5] highlighting the importance of treatment optimization among older patients. To that end, are there patients for whom radiotherapy can be "omitted"?

Among patients at least 60 years old, the Nordic trial demonstrated that outcome with temozolomide (or hypofractionated RT) alone was superior to a standard, aggressive, 6-week course of RT.[4] Similarly, among patients over 65 years old, the Neurooncology Working Group (NOA) of the German Cancer Society Study 8 (NOA-08) also compared temozolomide (using a dose-dense regimen of 100 mg/m^2 days 1–7/14) with standard course of RT (6 wk); at the time of first publication, there was no significant difference in survival (~9 mo) between arms, supporting the interpretation that temozolomide was non-inferior to RT.[6] Both the Nordic and NOA-08 trials also confirmed a strong predictive role for O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation status. Taken together, the application of *MGMT* to treatment decisions in older patients, and deferring RT among those with *MGMT* methylated tumors (m*MGMT*), emerged as a potential de-intensification strategy, particularly as *MGMT* appears most predictive in the isocitrate dehydrogenase (*IDH*) wild-type setting, which is nearly universal among older patients.[7] However, NOA-08 results were immature at initial publication; most notably, median survival was not reached for patients with m*MGMT* randomized to temozolomide.[6]

Now, important and updated results from NOA-08[8] reinforce and expand on the earlier conclusions. After a median follow-up of 7.5 years, 99% of patients have died,[8] compared with 2.1 years and 61% at original publication.[6] Patients with m*MGMT* treated with dose-dense temozolomide lived twice as long as those treated with standard RT (overall survival = 18.4 vs 9.6 mo, hazard ratio = 0.44, $P < 0.001$).[8] Whether the same or a similar benefit would be observed with less aggressive (and less toxic) standard temozolomide schedules remains unknown. Comparisons of temozolomide against shorter courses of RT that became more common since the trial launched were also not part of the NOA-08 design, nor were combinations with RT. However (and while cross-trial comparisons should always be viewed askance), median survival among older patients with m*MGMT* following treatment with temozolomide alone in NOA-08 (18.4 mo)[8] appears at worst no shorter and perhaps longer than chemoradiotherapy (with hypofractionated RT) in CCTG CE.6/EORTC 26062 (13.5 mo).[3] In addition to the benefit of avoiding RT-induced toxicities, deferring RT altogether also reduces the number of trips to the medical center, which may be particularly important in older patients with impaired mobility. (In today's climate, the concentrated risk of death from acquiring nosocomial coronavirus disease 2019, ie, COVID-19, during frequent in-person encounters must also be considered.[9]) There are several confounders, including the potential impact of crossover to RT at time of progression in NOA-08, potential imbalance of extent of resection and other prognostic factors, the relatively small sample size of various biomarker driven post-hoc analyses, and even different representations of methylation subgroups. These details do matter. Nonetheless, additional studies are unlikely to change our conclusion that deferring RT in favor of temozolomide alone in

older patients with m*MGMT* is now well justified at a macro level when we consider the totality of the data from multiple studies. Accordingly, our approach for elderly patients is to start temozolomide while *MGMT* results may be pending, consult with radiation oncology to plan RT, but only initiate concurrent RT (hypofractionated) if *MGMT* methylation is not detected. A supplemental step to consider is confirmation of *MGMT* results by at least 2 independent assays before deferring RT because discordance among laboratories is frequent (Roger Stupp, personal communication).

Perhaps most intriguing were the advanced analyses of interactions among *MGMT* methylation and broader methylation subgroups by the NOA-08 investigators. They demonstrated that the power of *MGMT* as a predictive biomarker depends heavily on methylation subtype. For example, benefit of temozolomide was most pronounced among cases with the "receptor tyrosine kinase (RTK) II" subtype.[8] As methylation profiling of gliomas becomes more common, these subgroups may also drive clinical decisions.

One other observation deserves mention in our view. We find it curious that older patients with *MGMT* methylated tumors benefit most from temozolomide despite a negligible frequency of *IDH* mutations, whereas results from the CATNON (EORTC study 26053–22054) trial suggest that patients with *IDH* wild-type tumors do not benefit from temozolomide at all.[10] It is possible that differences in histology may help explain the contradiction: most patients in NOA-08 had GBMs, whereas CATNON accrued only patients with anaplastic gliomas. Differences in methylation subclass may also play a role. Nonetheless, the paradox remains unresolved at present. Further work in this area will illuminate us all as we strive to balance effect and side effect of typical therapies.

Keywords

elderly | glioblastoma | methylation | MGMT | radiotherapy | temozolomide

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