The INDIGO Illusion: The Evidence Still Supports Chemoradiation Therapy in Patients with Low-Grade Glioma

Following subtotal resection of a low-grade glioma in a patient over the age of 40 years, the standard treatment remains adjuvant radiation therapy (RT) followed by combination chemotherapy as per Radiation Therapy Oncology Group 9802 guidelines.[1,2] We would deliver 54 Gy in 30 fractions via intensity modulated RT. Our gross tumor volume would consist of the surgical cavity, areas of contrast enhancement on T1-weighted magnetic resonance imaging, and residual fluid-attenuated inversion recovery changes. We would generate our clinical target volume by expanding our gross tumor volume by 1 to 1.5 cm (while respecting anatomic boundaries).

While age >40 years was considered a high-risk feature in Radiation Therapy Oncology Group 9802 guidelines, the role of adjuvant chemoradiation therapy after gross total resection remains an area of debate. However, patients should be informed about the high risk of recurrence associated with observation. Given this patient's relatively young age, the benefits and risks of adjuvant RT followed by combination chemotherapy should be discussed with him.

Nonenhancement does not imply benign or nonaggressive behavior. Thus, patients with nonenhancing tumor recurrence after an initial gross total resection should be considered for re-resection. Should a patient not be a surgical candidate, chemoradiation therapy should be offered.

Lastly, we do not apply the results of the INDIGO trial to our practice. Despite the fact that all enrollees had macroscopic disease, the trial compared vorasidenib to placebo rather than chemoradiation therapy as the standard of care. This was a significant methodological failure and limited the value of the trial's results.[3] Until robust comparative evidence establishes at least noninferiority, vorasidenib should not be used in lieu of chemoradiation therapy.

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INDIGO and Beyond: Approaching Vorasidenib With Cautious Optimism

There is no consensus on the optimal timing of adjuvant treatment after resection for grade 2 IDH mutant astrocytoma.[1] The EORTC 22845 randomized trial showed that early radiation therapy (RT) improved progression-free survival (PFS) but not overall survival (OS).[2] This patient has both "high-risk" (postoperative residue) and "low-risk" (no neurological deficits, no enhancement, grade 2 histology, and no *CDKN2A* deletion) features, allowing for different approaches to be considered. If additional "high-risk" factors (eg, significant postoperative volume, rapid growth) are present, I would recommend adjuvant RT (54 Gy in 30 fractions) followed by 6 cycles of procarbazine, CCNU, and vincristine (RTOG 9802) or 12 cycles of temozolomide (extrapolated from CATNON). If no further "high-risk" features are identified, options include watch-and-wait or vorasidenib. A short observation period may help in assessing postoperative tumor growth to guide decision.

I would recommend a watch-and-wait approach. In IDH mutant gliomas, recent data suggest that age is not a key predictor of adverse outcomes[3]; therefore, I would not consider this patient "high-risk." While the US Food and Drug Administration (FDA) label for vorasidenib includes patients with gross total resection (GTR), supporting data remain limited. Some patients with GTR may achieve prolonged PFS without adjuvant treatment, making the risk-benefit balance for this population uncertain.

I would recommend considering a new surgery if feasible; otherwise, vorasidenib based on the INDIGO trial results.

I recommend vorasidenib for patients with residual/recurrent grade 2 IDH mutant gliomas not in immediate need of RT or chemotherapy. INDIGO showed it prolongs PFS and delays further treatment without affecting quality of life. A brief postsurgical period allows for stabilization of scarring, though a full year is not necessarily required. I continue treatment until progression, unacceptable toxicity, or patient decision. Fertility preservation should be discussed before starting treatment for eligible patients.

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