IDH mutant low-grade glioma

Diffuse astrocytoma IDH mutant.

Gemistocytic astrocytoma IDH mutant.

Oligodendroglioma IDH mutant and 1p/19 q codeleted.

Treatment

The level of evidence for adjuvant treatment of diffuse WHO grade II glioma (low-grade glioma, LGG) is low. In so-called "high risk low-grade glioma" patients most centers currently apply an early aggressive adjuvant therapy after surgery. The aim of a assessment was to compare progression free survival (PFS) and overall survival (OS) in patients receiving radiation therapy (RT) alone, chemotherapy (CT) alone, or a combined/consecutive RT+CT, with patients receiving no primary adjuvant treatment after surgery.

Based on a retrospective multicenter cohort of 288 patients (≥ 18 years old) with diffuse WHO grade II gliomas, a subgroup analysis of patients with confirmed isocitrate dehydrogenase mutation was performed. The influence of primary adjuvant treatment after surgery on PFS and OS was assessed using Kaplan-Meier estimates and multivariate Cox regression models, including age (≥ 40 years), complete tumor resection (CTR), recurrent surgery, and astrocytoma versus oligodendroglioma.

One hundred forty-four patients matched the inclusion criteria. Forty patients (27.8%) received adjuvant treatment. The median follow-up duration was 6 years (95% confidence interval 4.8-6.3 years). The median overall PFS was 3.9 years and OS 16.1 years. PFS and OS were significantly longer without adjuvant treatment ($p = 0.003$). A significant difference in favor of no adjuvant therapy was observed even in high-risk patients (age ≥ 40 years or residual tumor, 3.9 vs 3.1 years, $p = 0.025$). In the multivariate model (controlled for age, CTR, oligodendroglial diagnosis, and recurrent surgery), patients who received no adjuvant therapy showed a significantly positive influence on PFS ($p = 0.030$) and OS ($p = 0.009$) compared to any other adjuvant treatment regimen. This effect was most pronounced if RT+CT was applied ($p = 0.004$, hazard ratio [HR] 2.7 for PFS, and $p = 0.001$, HR 20.2 for OS). CTR was independently associated with longer PFS ($p = 0.019$). Age ≥ 40 years, histopathological diagnosis, and recurrence did not achieve statistical significance.

In this series of IDH-mutated LGGs, adjuvant treatment with RT, CT with temozolomide (TMZ), or the combination of both showed no significant advantage in terms of PFS and OS. Even in high-risk patients, the authors observed a similar significantly negative impact of adjuvant treatment on PFS and OS. These results underscore the importance of a CTR in LGG. Whether patients ≥ 40 years old should receive adjuvant treatment despite a CTR should be a matter of debate. A potential tumor dedifferentiation by administration of early TMZ, RT, or RT+CT in IDH-mutated LGG should be considered. However, these data are limited by the retrospective study design and the potentially heterogeneous indication for adjuvant treatment [1].

Case series

Miller et al., retrospectively analyzed 275 IDH mutant glioma patients treated at the Massachusetts General Hospital. Progression was determined using low-grade glioma RANO criteria. They calculated survival statistics with the Kaplan-Meier method and survival proportions were correlated with molecular, histologic and clinical factors.

During a median follow-up of 6.4 years, 44 deaths (7.6%) and 149 first progression (PFS1) events (54.1%) were observed. Median PFS1 was 5.7 years (95% CI 4.7-6.4) and OS was 18.7 years (95% CI 12.2 years - not reached). Consistent with prior studies, we observed an association of grade, molecular diagnosis and treatment with PFS1. Following the first progressive episode, 79 second progression events occurred during a median follow-up period of 4.1 years. Median PFS following an initial progressive event (PFS2) was accelerated at 3.1 years (95% CI 2.1-4.1). PFS2 was a surrogate prognostic marker, identifying patients with poorer overall survival.

They reported outcomes in a large cohort of IDH mutant glioma, providing a well-characterized historical control population for future clinical trial design. Notably, the interval between first to second recurrence (PFS2 - 3.0 years) is shorter than time from diagnosis to first recurrence (PFS1 - 5.7 years), evidence that these tumors clinically degenerate from an indolent course to an accelerated malignant phase. Thus, PFS2 represents a relevant outcome for trials investigating drug efficacy at recurrence [2].

References

1)
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2)
Miller JJ, Loebel F, Juratli TA, Tummala SS, Williams EA, Batchelor TT, Arrillaga-Romany I, Cahill DP. Accelerated progression of IDH mutant glioma after first recurrence. Neuro Oncol. 2019 Jan 22. doi: 10.1093/neuonc/noz016. [Epub ahead of print] PubMed PMID: 30668823.