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.

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
