The role of chemotherapy in low grade glioma after the new WHO classification

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LGG represents a spectrum of tumor types with diverse histologic features; however, recently molecular analysis of tumors has become a critical part of tumor classification and prognostication. In 2016, the WHO updated its classification of primary brain tumors to include molecular characterization, now defining tumors both on phenotype and genotype. Oligodendrogliomas on traditional hematoxyline and eosin (H&E) staining have round nuclei and fine delicate branching vessels, but are now defined as having both an isocitrate dehydrogenase (IDH) gene family mutation and combined whole-arm losses of 1p and 19q (1p/19q codeletion). Astrocytomas are characterized by prominent glial fibrillary acidic protein processes, typically also have mutations in IDH, but have intact 1p and 19q chromosomes as well as loss of ATRX. Mutations in either IDH1 or IDH2 occurs in up to 80% of grade II and III diffuse gliomas and carries a more favorable prognosis compared to IDH wild-type tumors. Several studies have now performed large-scale whole-genome sequencing on LGG. The Cancer Genome Atlas (TCGA) Research Network analyzed 293 lower-grade gliomas from adults, incorporating exome sequence, DNA copy number, DNA methylation, messenger RNA expression, microRNA expression, and targeted protein expression and found three prognostically significant subtypes of lower-grade glioma (grade II and III) that were more concordant with molecular signature of IDH, 1p/19q, and TP53 status than with histologic class. Patients with lower grade gliomas with mutations in IDH and had 1p/19q co-deletion had the most favorable prognosis and were also associated with mutations in CIC, FUBP1, NOTCH1, and the TERT promoter. Patients in the intermediate prognostic class had tumors characterized by IDH mutations without 1p/19q co-deletion and were associated with mutations in TP53 (94%) and ATRX inactivation (86%). The patients with the least favorable outcomes consisted of LGGs without IDH mutations and had mutations in PTEN, EGFR, NF1, TP53, PIK3Ca, PTPN11 and PLCG1, and were molecularly similar to WHO grade IV glioblastomas. A separate analysis by Mayo-UCSF, five molecular subtypes were found based on IDH, 1p/19 co-deletion, and TERT promoter mutation status in 1087 gliomas: triple-positive (mutations in both TERT and IDH plus 1p/19q co-deletion), mutations in both TERT and IDH, mutation in IDH only, mutation in none of the three, and mutation in TERT only.

It remains to be determined the precise optimal management of patients with LGG. Treatment recommendations are currently evolving, mainly because of a change in the prognostic factors that are based on molecular and cytogenetic features. Standard of care includes maximal safe surgical resection. Prior randomized clinical trials stratified treatment arms based on extent of resection and age, with patients stratified into low risk (age less than 40 and gross total resection) and high risk (age greater than 40 or subtotal resection). Patients who are low risk based on these criteria may undergo routine MRI surveillance following resection. This study however did not address the management of patients with LGG in the era of genomic medicine. For example, a patient less than 40 years of age with a grade II astrocytoma with wild
type IDH status would no longer be considered “low risk” even if a gross total resection was performed. These patients are known to have a poor prognosis and observation may not be prudent, and in these cases, immediate radiation with concomitant chemotherapy may be utilized. It is important that patients undergo long term close surveillance as recurrence is nearly universal.

The risk benefit ratio of treatment with radiation and chemotherapy must be weighed for each individual patient. A large phase 3 trial (RTOG 9802) that was initiated in 1998 randomized patients with high-risk LGG (patients older than 40 years or with subtotal resection) to radiation alone or radiation plus chemotherapy consisting of PCV. Results with follow-up of a median of 11.9 years demonstrate a significant benefit in overall survival in patients treated with both radiation plus chemotherapy compared to radiation alone. The overall survival was 7.8 years for patients treated with radiation alone, compared to 13.3 years for patients treated with both radiation and chemotherapy. Progression-free survival at 10 years was 21% in the patients that received radiation alone, compared to 51% in the patients that received both radiation and chemotherapy. The benefit of radiation and chemotherapy was seen in all histologic subgroups evaluated, but did not reach significance in patients with astrocytoma. Further studies are underway investigating the molecular subtypes of tumors that derive the greatest benefit from chemotherapy and radiation at initial diagnosis, however, results thus far suggest responses irrespective of 1p/19q status. The limitations of these retrospective post hoc analyses based on the molecular and cytogenetic analysis is the lack of tissue availability for the majority of the patients who were enrolled in the study. Based on the results of this study, patients with high risk LGGs characterized by older age or subtotal resection should strongly consider a combination of radiation and chemotherapy at initial diagnosis. In high risk patients with a more prognostically favorable oligodendroglioma diagnosis, if there is concern for long term effects of radiation, one could consider treatment with chemotherapy alone at initial diagnosis.

A large phase 3 trial (EORTC 22033-26033) investigated standard radiation therapy compared to 1 year of temozolomide in patients with high-risk LGGs. High risk in this particular study is defined as patients older than age 40, symptomatic, or patients with tumors growing under observation. Preliminary data from this study after a median follow-up of 45.5 months suggests there is no significant difference in progression-free survival between the two groups (47 months in the RT arm and 40 months in the temozolomide arm). Progression-free survival, however, is longer in the radiation treatment group compared to treatment with temozolomide for the subgroup of patients with IDH mutations but without co-deletion of 1p/19q, consistent with patients with astrocytoma. The limitation of this report however is the short followup in terms of survival endpoints for the study. It is important to note that RT alone cannot be considered the current “standard of care” treatment for high risk LGG based on the recent publication of the results of RTOG 9802.

References

