Neuro-oncology

Five new things

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Summary

Recent reports herald important advances in our understanding and management of gliomas. A role for alkylator chemotherapy in the management of certain high-grade gliomas has been confirmed and linked to specific, clinically ascertainable molecular markers. Magnetic resonance spectroscopy can now image 2-hydroxyglutarate, an oncometabolite restricted to the three-quarters of low-intermediate grade gliomas harboring an isocitrate dehydrogenase gene mutation; this has powerful implications for diagnosis and assessment of response to therapies. Genome-wide association studies point to several SNPs conveying increased risk of glioma; further studies of the involved genes and RNA products will enhance our understanding of glioma development. Finally, high-throughput sequencing has identified novel mutations in a histone-coding gene and in genes related to the histone complex in pediatric glioblastoma.

We report recent advances in the field of neuro-oncology.

Chemotherapy for anaplastic oligodendrogliomas

Diffuse infiltrating gliomas in adults comprise grade II (“low-grade”), grade III (“anaplastic”), and grade IV (“glioblastoma”) gliomas. Grade II and III tumors may be pure astrocytomas, pure oligodendrogliomas, or mixed; it has long been recognized that oligodendrogliomas have a more favorable prognosis than astrocytomas, with mixed tumors having an intermediate outcome. The majority of

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pure anaplastic oligodendrogliomas, and a sizeable minority of mixed anaplastic gliomas, have deletions of chromosomes 1p and 19q.

With the realization that tumors with an oligodendroglial component often responded to salvage chemotherapy for postradiation progression, in 1994, American (Radiation Therapy Oncology Group [RTOG]) and European (European Organization for Research and Treatment of Cancer [EORTC]) clinical trial groups launched randomized phase III studies of radiation therapy (RT) and chemotherapy (procarbazine, CCNU, and vincristine, or PCV) for newly diagnosed anaplastic gliomas containing an oligodendroglial component. The trials had similar design, though RTOG 9402 administered PCV before RT and EORTC 26951 after RT. In 1998, Cairncross et al.¹ demonstrated that codeleted anaplastic oligodendrogliomas were much more likely to respond to salvage PCV than undeleted tumors. Investigators then added plans to analyze trial outcomes based on deletion status.

The initial reports of RTOG 9402 and EORTC 26951, published in 2006, yielded concordant results.^{2,3} Both studies found much longer survival in patients harboring 1p/19q codeletion regardless of treatment assignment. Both studies reported prolonged progression-free survival in the PCV arms but no improvement in overall survival, suggesting patients could be effectively salvaged with chemotherapy following postradiotherapy progression. Although the benefit in progression-free survival appeared principally in patients with 1p/19q codeletion, there was no suggestion at 7 years of follow-up that patients with codeleted tumors receiving early PCV lived longer than those receiving delayed chemotherapy. Of note, however, the median survival of codeleted patients had not yet been reached.

Against this backdrop, updated reports of these trials in 2012 generated a surprise. In RTOG 9402, patients with codeleted tumors randomized to RT/PCV lived twice as long as those randomized to RT alone (14.7 vs 7.3 years, $p < 0.001$).⁴ The smaller EORTC trial demonstrated a similar trend to improved survival in codeleted patients randomized to PCV (hazard ratio 0.56, 95% confidence interval 0.31–1.03).⁵ Patients lacking codeletion continued to derive no survival benefit from early PCV.

Despite the caveats that the original studies were not designed to analyze the predictive or prognostic benefit of 1p/19q codeletion, rendering these retrospective analyses, and patient numbers in both studies were small, the concordant findings strongly suggest that RT alone is no longer a sufficient therapy for codeleted anaplastic gliomas. The unanticipated results have led to a halt in the ongoing international CODEL trial for codeleted anaplastic gliomas, which was randomizing patients to a radiation-alone control arm vs radiation combined with temozolomide (with a small exploratory chemotherapy-alone arm with temozolomide). One pressing question is whether patients should receive radiation plus PCV vs radiation plus temozolomide; temozolomide is far better tolerated than PCV and has a superior track record with radiation for newly diagnosed glioblastoma. Another question is whether a chemotherapy-alone approach would allow for meaningful deferral of radiation and its potential delayed neurocognitive sequelae. Ongoing discussions will lead to redesign of the CODEL trial.

Management of the elderly patient with glioblastoma

Age is a powerful prognostic factor in glioblastoma, with elderly patients faring particularly poorly. In 2004, results of an EORTC/NCIC clinical trial established the combination of radiation and temozolomide as standard of care for newly diagnosed glioblastoma and suggested

that tumors with inactivation of the DNA damage repair protein *MGMT* via methylation of the gene's promoter were most sensitive to temozolomide. However, this pivotal trial excluded patients older than 70, and subgroup analysis showed marginal apparent benefit from temozolomide in patients older than 60, and especially 65. Was this due to inadequate power from low numbers, and should we be using temozolomide in the elderly? A second issue is whether elderly patients are better served with compression of the standard 6-week radiation course into a more patient-friendly 2 to 3 weeks.

Recently published clinical trials shed light on these issues without providing resolution. The NOA-08 study asked whether dose-dense temozolomide was noninferior to standard radiation in patients 65+ with glioblastoma or anaplastic astrocytoma.⁶ Almost 400 patients (89% glioblastoma) were randomized; the majority of patients received the alternative treatment at tumor progression. Overall survival and time to tumor progression were slightly but not significantly better in the radiation arm. NOA-08 confirmed that *MGMT* promoter methylation is associated with improved survival; more interesting was the finding that *MGMT* status might predict optimal therapy. Among patients with promoter-methylated tumors, progression-free survival was longer with temozolomide (8.4 vs 4.6 months), whereas promoter-unmethylated tumors remained progression-free longer with radiation (4.6 vs 3.3 months). While study limitations included the mixture of tumor grades and the availability of *MGMT* status in only 56%, results support routine *MGMT* testing and suggest patients with promoter-methylated tumors may be undertreated with radiation alone.

The Nordic trial randomized approximately 300 elderly glioblastoma patients (median age 70) to either standard temozolomide for up to 6 4-week cycles, standard 6-week/60 Gy radiation, or 34-Gy radiation administered over 2 weeks (hypofractionation).⁷ Median survival was significantly worse in the standard radiation arm (6.0 months) than in the temozolomide or hypofractionated radiation arms (8.3 and 7.5 months). Within the temozolomide arm, survival was substantially better in promoter-methylated tumors. The authors concluded that either temozolomide or hypofractionated radiotherapy should be considered standard options in the elderly, and that *MGMT* status might predict benefit from temozolomide. A major study shortcoming was the failure to determine progression-free survival, leaving open the possibility that relatively effective salvage therapy might have altered the importance of initial treatment arm assignment. Low power because of slow patient accrual was also an issue.

Both of these studies support the role of *MGMT* testing and suggest that temozolomide monotherapy is a reasonable option in the elderly patient with *MGMT* promoter methylation, as did another recent study.⁸ The Nordic trial confirms that short-course radiation is a valid treatment option in this population.⁹ Left unanswered is whether combined temozolomide and radiation, either standard or hypofractionated, might benefit some elderly patients, such as those with promoter-methylated tumors. Neuro-oncologists hope that an ongoing international study answers this question: NCIC CTG CE.6 is randomizing 560 elderly (>65) patients to hypofractionated radiation (40 Gy/15 fractions) with or without temozolomide and includes comprehensive molecular analysis including tumor *MGMT* status.

Molecular imaging to detect *IDH* mutations

One of the most surprising and important findings to arise from high-throughput sequencing of cancers has been the recognition that three-quarters of grade II and III gliomas (as well as some leukemias and cartilaginous tumors) harbor mutations of isocitrate dehydrogenase (*IDH*). *IDH* mutations appear to precede the 1p/19q codeletion found in most oligodendrogliomas and the *TP53* mutations in astrocytomas, suggesting they represent an early step in gliomagenesis. Isocitrate dehydrogenase catalyzes the oxidative decarboxylation of isocitrate to α -ketoglutarate, with *IDH1* found in the cytoplasm and peroxisome and *IDH2* in mitochondria. In gliomas, most mutations arise in the active site of *IDH1*, with a small percentage affecting the active site of *IDH2*. *IDH* represents the most frequently mutated metabolic enzyme in human cancer.

Figure The result of inhibition of α -ketoglutarate-dependent dioxygenases in the setting of IDH mutation is increased DNA and histone methylation

An explosion of research efforts quickly revealed that these mutations result in neomorphic enzyme function, in which IDH no longer catalyzes conversion of isocitrate to α -ketoglutarate but rather converts α -ketoglutarate to 2-hydroxyglutarate (2-HG). The oncometabolite 2-HG acts as an antagonist of α -ketoglutarate for a set of α -ketoglutarate-dependent dioxygenases (figure). These include histone demethylases as well as DNA hydroxylases that serve to demethylate DNA. Consequently, *IDH*-mutated gliomas manifest DNA hypermethylation. Perhaps as a result of the ensuing transcriptional perturbation, *IDH*-mutated gliomas have a more favorable prognosis grade-for-grade than *IDH*-intact counterparts. 2-HG levels are extremely low in the normal brain but are elevated up to 3 orders of magnitude in the setting of *IDH* mutation. Consequently, 2-HG levels might serve as biomarkers of the prognostically important *IDH* mutation.

Recent publications suggest that 2-HG levels in gliomas can be determined noninvasively and are tightly correlated with the presence of *IDH* mutation. Two studies overcame the technical challenge of differentiating 2-HG from glutamate, glutamine, and GABA in brain tissue and have shown a high correlation between the presence of 2-HG in glioma tissue samples determined by magnetic resonance spectroscopy (MRS) and the presence of *IDH* mutation.^{10,11} Moreover, normalizing for tumor cellularity, 2-HG production appeared stable over different grades of *IDH*-mutated gliomas, suggesting that MRS might allow for spatial characterization of gliomas.¹⁰

Even more exciting is work indicating *IDH* mutational status of lesions can be ascertained noninvasively in vivo with MRS. Utilizing a 3-T magnet, Choi et al.¹² were able to detect 2-HG on MRIs of patients with *IDH*-mutated gliomas and correlate this with both *IDH* mutation by gene sequencing and the presence of 2-HG in tumor tissue acquired from these patients, a finding another group has confirmed.¹³ Their methodology appeared highly sensitive and specific. They also developed multivoxel imaging of 2-HG, so in one case they could show a crude 2-HG map of the tumor.

The ability to noninvasively detect and monitor 2-HG with MRS provides remarkable opportunities. Since 2-HG is not detected in blood, urine, or CSF of patients with *IDH*-mutated gliomas, MRS would allow conclusive determination that an unbiopsied intracranial lesion represents a glioma. If and when 2-HG mapping advances, this may provide a new means of monitoring the response of an *IDH*-mutated glioma to therapy. Finally, inhibitors of mutated IDH are in development and have shown promise in animal studies¹⁴; the ability to determine that such agents are reaching and inhibiting the target without sampling tissue would enormously benefit human clinical trials.

Genome-wide association studies in gliomas

The cause of gliomas remains elusive. The only well-accepted environmental risk factor for gliomas is a remote prior history of ionizing radiation to the head, and this factor applies

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to a tiny percentage of patients. Clearly defined inherited susceptibility syndromes, including neurofibromatosis type I, Li-Fraumeni, Turcot, Lynch, and melanoma-astrocytoma syndromes, similarly account for a minute fraction of cases. It is also recognized that gliomas occasionally cluster in families, and that 5%–10% of patients with glioma have a positive family history; studies have consistently shown glioma risk is elevated twofold in first-degree relatives of glioma patients.

Prior to the advent of genome-wide association studies (GWAS), studies seeking a genetic basis for gliomas focused on a candidate gene approach based on specific genes in targeted pathways (for example, those involved in the cell cycle or DNA repair).¹⁵ These studies failed to identify any definite susceptibility alleles.

Comprehensive mapping of human haplotypes with single nucleotide polymorphisms (SNPs) and copy number polymorphisms now allow GWAS to look for common susceptibility alleles with low effect sizes in a cost-effective manner.^{15,16} The unbiased, agnostic nature of this approach is desirable given biological complexity and the previous failure of more directed strategies. In general, cancer GWAS have found minor frequency alleles (MAF) associated with a relative risk of 1.1 to 1.4.¹⁶ Typically the MAF is >10% given the limitation of sample sizes.

In 2009, 2 groups identified SNPs associated with an increased risk of gliomas.^{17,18} One site on chromosome 9p occurred within the noncoding region of *CDKN2B*, a known tumor suppressor gene coding for a protein that blocks progression through cell cycle. A second site that both groups identified was on chromosome 20q, in a noncoding portion of *RTEL1*. This DNA helicase is critical for regulation of telomere length, and its loss is associated with shortened telomere length, chromosome breaks, and translocations. SNPs in a second telomere-associated gene, *TERT*, also showed an association with glioma risk; *TERT* codes for human telomerase, a protein that maintains telomere length whose activity is increased in glioblastoma. Relative risk for glioma with the identified alleles was generally ≤ 1.4 , on par with GWAS in other malignancies.

Recently, a remarkably powerful glioma susceptibility SNP has been identified. Through a combination of genotyping and next-generation sequencing, Jenkins et al.¹⁹ found that the “G allele” of rs55705857 was associated with a sixfold higher incidence in cases with oligodendrogliomas. A similar odds ratio (OR) existed between this allele and *IDH*-mutated astrocytomas. This allele did not confer an increased risk of *IDH*-wild type glioblastomas or astrocytomas. Roughly 40% of patients with oligodendrogliomas or *IDH*-mutated astrocytomas carry at least one G risk allele at rs55705857 compared to approximately 8% of controls. Only 2 other associations with an OR >4 are recognized in any malignancy: one for the development of familial melanoma and one for outcome in chemotherapeutically treated lung cancer.

The mechanism by which this allele increases glioma susceptibility, specifically to histologic/molecular subtypes, remains unknown. The risk region is believed to correspond to a highly conserved presumed long noncoding or microRNA. Further efforts to elucidate its role promise to enhance our understanding of the role of *IDH* mutation, and perhaps DNA hypermethylation in general, in gliomagenesis.

Histone 3.3 mutations and related genetic aberrations in pediatric glioblastoma

One of the most dramatic new findings in glioblastoma genetics in recent years has arisen from profiling of pediatric glioblastoma. It has long been clear that the underlying genetic lesions in pediatric glioblastoma differ from those in adult glioblastoma, including a lack of epidermal growth factor receptor mutations/amplifications. However, potential drivers of pediatric glioblastoma remained poorly characterized until the recent exomic sequencing of 48 pediatric glioblastomas.²⁰ Mutations were identified in the gene *H3F3A* coding for histone 3.3, and in the functionally associated genes *ATRX* and *DAXX*, in 44% of pediatric glioblastoma. A separate report confirmed H3.3 mutations in pediatric glioblastoma, in addition to identifying H3.3 mutations (and also mutations in the similar histone H3.1) in most cases of pediatric diffuse intrinsic pontine glioma.²¹

These findings represent the first example of mutation in a histone gene identified in cancer. Two specific mutations comprised nearly all of those found in H3.3, a lysine 27-to-methionine mutation (K27M), and a slightly less frequent guanine 34-to-arginine mutation (G34R).²⁰ A later report indicated that K27M glioblastomas are typically found in the midline, while G34R glioblastomas tend to be located in the cerebral hemispheres.²² Interestingly, the H3.3 mutations were discovered alongside others frequently found in association, in the genes *ATRX* and *DAXX* (α -thalassemia/mental retardation syndrome X-linked and death-domain associated protein, respectively).²⁰ These proteins are components of a complex incorporating H3.3 at pericentric chromatin regions or at telomeres, the regions capping the ends of chromosomes and linked to some of the glioma-predisposing SNPs found in the GWAS described earlier. In keeping with a connection to telomeres, mutations in *ATRX* were associated with a process called alternative lengthening of telomeres (ALT), by which telomeres are lengthened in cancers without overexpression of the *TERT* gene.²⁰ Extending this to adult glioma, *ATRX* mutations or loss of expression were later found in 33% and 46% of adult grade 2 and 3 gliomas, respectively—always in astrocytoma or oligoastrocytoma, never in oligodendroglioma—and in 80% of secondary glioblastoma.²³ In addition to its potential relevance in astrocytoma biology, *ATRX* mutation might also be useful as an immunohistochemical marker in a panel to distinguish astrocytoma from oligodendroglioma.

Is the functional relevance of these mutations to modify DNA methylation, histone methylation, telomeres, or some combination of these? Subsequent reports have extended the initial findings and may help answer this key question. DNA methylation profiles were found to differ in glioblastomas with *H3F3A* K27M mutations, *H3F3A* G34R mutations, and the *IDH1* mutations described earlier.²¹ The G34R mutation correlates with hypomethylation near chromosome ends, which may be a trigger for ALT.²¹ All of these mutations may affect histone 3.3 methylation at lysine 27 or lysine 36; H3.3 K36 methylation is also modified by *IDH1* mutation and by newly identified mutations in the H3K36 trimethyltransferase *SETD2*—found in 15% of pediatric high-grade glioma and nonoverlapping

Neuro-oncology: Five new things

- The addition of alkylator-based PCV chemotherapy has been shown to produce an overall survival benefit compared to radiotherapy alone in the subset of anaplastic oligodendroglial tumors harboring 1p/19q codeletion.
- Two studies of glioblastoma in the elderly support the routine testing of MGMT promoter methylation status, with temozolomide alone yielding a better outcome than radiotherapy for promoter-methylated tumors.
- New magnetic resonance spectroscopy techniques can detect the metabolite 2-hydroxyglutarate produced by the isocitrate dehydrogenase mutation found in most lower-grade diffuse gliomas, offering potential both for noninvasive confirmation that an imaging abnormality is a glioma and for monitoring response to therapy.
- Genome-wide association studies have identified several SNPs associated with an increased risk of developing gliomas, including one that increases the risk of developing an oligodendroglioma or IDH-mutated astrocytomas a remarkable sixfold.
- Mutations are present in the gene *H3F3A* coding for histone 3.3, and in the functionally associated genes *ATRX* and *DAXX*, in 44% of pediatric glioblastoma, representing the first mutation in a histone gene reported in cancer.

with H3.3 mutations.²⁴ Translating these remarkable new findings to novel therapeutic approaches, the ultimate goal, may thus depend on modifying aberrant histone 3.3 methylation at these sites.

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