Chemotherapy for Low-Grade Gliomas: Lessons and Questions

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As our understanding of tumor biology grows, we may identify targeted agents that can be used to treat low-grade gliomas. One such approach moving into clinical trials is the use of IDH inhibitors.

For decades, the role of chemotherapy in the management of gliomas has been controversial. In 2005, Stupp et al[1] presented the first convincing data that the addition of chemotherapy (temozolomide) to radiation therapy (RT) increased median survival by 2.5 months compared with RT alone, leading to a new “standard of care” for glioblastoma multiforme. A similar effect of chemotherapy was reported in 2013, when mature data from Radiation Therapy Oncology Group (RTOG) trial 9402 and European Organisation for Research and Treatment of Cancer (EORTC) trial 26951 revealed that the addition of PCV (procarbazine, lomustine [CCNU], and vincristine) to RT significantly increased overall survival in patients with codeleted anaplastic oligodendrogliomas (AOs) or anaplastic oligoastrocytomas (AOAs) compared with RT alone.

Indeed, in RTOG 9402, median survival increased by 7.4 years in patients randomized to PCV-RT, compared with those treated with RT alone; and in EORTC 26951, at a median follow-up of 11.7 years, the median survival time was not reached in the PCV-RT arm but was 9.3 years in the RT arm.[2,3] In elderly patients with methylated glioblastoma multiforme, chemotherapy alone was also found to be a better treatment strategy compared with RT alone or chemoradiation.[4,5] In 2014, data from RTOG 9802 again showed the impact of adding PCV to RT for treatment of high-risk, low-grade gliomas; patients ≥ 40 years of age or < 40 years with subtotal tumor resection showed a 5.5-year increase in survival time with the addition of PCV to RT.[6] The data from these trials clearly show that chemotherapy has a role in the treatment of gliomas.

In their article in this issue of ONCOLOGY, Strowd et al have focused on the role of chemotherapy in low-grade gliomas.[7] There is concern regarding potential toxicities arising from treatment of low-grade gliomas in younger patients, who will have relatively long survival times, compared with patients with malignant gliomas, in whom survival duration is often short. Treatment-related toxicities include radiation-induced cognitive changes (leukoencephalopathy) or chemotherapy-induced myelodysplastic syndrome or leukemia. These toxicities can have a dramatic impact on patients’ quality of life. More recently, there are data indicating treatment of low-grade gliomas with temozolomide can lead to a hypermutated phenotype and drive malignant transformation.[8] These issues need to be considered when making treatment decisions, given that in some cases, it might be more prudent to delay treatment and instead follow the patient until the tumor grows or neurologic symptoms arise or worsen.

Despite recent positive data about chemotherapy, there are still many unknowns regarding management of low-grade gliomas. These include questions about timing of surgery and the extent of resection needed for optimal short-term and long-term benefit; timing of RT (early vs late); and choosing the optimal chemotherapy agent/regimen and most appropriate timing of treatment (ie, considering whether chemotherapy should be given pre-RT, concurrent with RT, post-RT, or in some combination of these options, and ascertaining whether upfront use of chemotherapy will allow RT to be delayed). In addition, the optimal timing of treatment for an asymptomatic low-risk patient needs to be defined—that is, should it be the same as for a high-risk patient?

While no prospective randomized data exist for timing of surgery, a study from Norway compared outcomes between two hospitals, one of which favored observation after biopsy while the other preferred resection.[9] Median survival was 5.9 years for patients managed with biopsy only, whereas after a median follow-up of 7 years, median survival was not reached for patients who underwent early resection. Estimated 5-year patient survival rates were 60% for biopsy and 74% for watchful waiting and early resection. Extent of resection also appears to have an impact on survival[10]; however, the optimal degree of resection for patient benefit remains to be determined. In glioblastoma multiforme, there are data indicating that patients who undergo > 90% extent of resection derive the most benefit, with benefit dropping off with lesser degrees of resection but still significant down to 78% extent of resection.[11] Data also exist for supramaximal resection, which
may lead to a delay in malignant transformation and postoperative treatment.[12] The Pignatti criteria have defined a high-risk group of low-grade glioma patients; these criteria include clinical factors with a negative impact on patient survival, such as age > 40 years, astrocytoma histology, tumor diameter > 6 cm, tumor crossing the midline, and presence of neurologic deficit before surgery.[13] Importantly, in the RTOG 9802 trial, not all of these factors were applied, which highlights the fact that low-grade glioma can be classified differently across trials. Molecular factors in low-grade glioma that correlate with survival include IDH mutations, promoter status of the MGMT gene, and the status of chromosomes 1p and 19q. Other molecular abnormalities common in low-grade glioma are mutations of p53, ATRX, CIC, and FUBP1, as well as an ALT (alternative lengthening of telomeres) phenotype. These mutations allow patients with low-grade gliomas to be categorized as having low-grade astrocytomas (IDH, p53, and ATRX mutations) or low-grade oligodendrogliomas (IDH, CIC, and FUBP1 mutations), which are associated with median survival times of 51 and 96 months, respectively, compared with 13 months for patients with neither of these phenotypes.[14,15] Patients with the c-GMP phenotype, which is associated with a proneural phenotype and IDH mutation, also have improved survival duration.[16] With the exceptions of 1p and 19q status—and MGMT gene promoter methylation and IDH mutation status—none of the studies showing a benefit of chemotherapy have stratified patients based on these newer molecular factors, which could define subgroups that are more responsive, or less responsive, to chemotherapy.[1,17-19]

Three seminal trials in low-grade glioma showed that high-dose RT does not improve survival but does increase CNS toxicity,[20,21] and delaying RT does not impact survival.[22] Until recent data from RTOG 9802 became available, RT was the mainstay of treatment for low-grade gliomas. Despite compelling data regarding the addition of chemotherapy to RT, as previously mentioned, what remains unclear is the optimal chemotherapy agent(s) to use for patients with low-grade gliomas, as well as the timing of treatment. Level 1 data from three trials indicate that PCV added to RT leads to a survival benefit. However, most physicians have adopted temozolomide as their main chemotherapy, given its improved tolerability compared with PCV. An obvious concern is whether increased tolerability would lead to a decrease in survival. Older data in malignant gliomas suggested PCV was better than BCNU (carmustine) for management of malignant gliomas[23]; however, upon analysis of a larger data set, this did not appear to be the case.[24] Other data comparing PCV against temozolomide also did not show a benefit to PCV.[25] While the data might suggest that a multidrug regimen is not inferior to single-agent therapy, this will need to be borne out in a randomized trial comparing RT + temozolomide vs RT + PCV; this assessment is currently underway as part of the COGEL trial in codeleted anaplastic oligodendrogliomas (ClinicalTrials.gov identifier NCT00887146). Importantly, however, this trial is not comparing RT followed by PCV or temozolomide but will assess outcomes with RT followed by PCV vs RT + temozolomide followed by adjuvant temozolomide. While this question is important, the data will take years to collect and need to be prioritized among all the novel emerging oncologic therapies that could lead to improved survival.

Nonetheless, we now know that chemotherapy, when added to RT, can improve survival in patients with low-grade gliomas. As molecular data from RTOG 9802 are analyzed, we may learn more about subgroups of responders and/or nonresponders. As our understanding of tumor biology grows, we may identify targeted agents that can be used to treat low-grade gliomas. One such approach moving into clinical trials is the use of IDH inhibitors (ClinicalTrials.gov identifiers NCT02273739 and NCT02073994).

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