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Old chemotherapy makes a comeback: dual alkylator therapy for pediatric high-grade glioma

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See the article by Jakacki et al., on pages 1442–1450

Pediatric high-grade glioma is an orphan disease with approximately 130 new cases of glioblastoma and 70 cases of anaplastic astrocytoma diagnosed annually in the USA in the 0–19 year age group, a much lower diagnosis rate than the approximately 6000 and 1200 cases identified, respectively, in the adult population.[1] In adults, the current standard of care of high-grade gliomas includes maximal safe surgical resection followed by radiation therapy with concurrent and adjuvant temozolomide (TMZ). This approach is based on the result of a large randomized study that has demonstrated a modest, yet significant survival advantage with TMZ in adult patients with newly diagnosed glioblastoma.[2] Yet, in the pediatric population, the management of high-grade gliomas remains controversial, the absence of large randomized studies preventing the emergence of a clearly defined standard of care.

During the last decade, the Children's Oncology Group conducted 2 nonrandomized studies for patients with newly diagnosed high-grade gliomas. The statistical design of these studies was similar: the primary objective was to determine whether the proposed treatment resulted in an improvement in event-free survival rate compared with that reported in historical controls. In the ACNS0126 trial, patients received concomitant TMZ with radiotherapy followed by 10 courses of adjuvant TMZ.[3] The results of this trial were disappointing, as TMZ did not seem to result in an improved outcome compared with the therapy provided in the previous Children's Cancer Group (CCG)-945 trial (used for historical comparison).[4]

In this context, the results of the Children's Oncology Group ACNS0423 study reported in this issue[5] are both unexpected and disturbing. Unexpected, as no one would have anticipated a survival benefit with the addition of an old drug to the combination of TMZ and radiation. Disturbing, as there is no clear explanation for this survival benefit. However, the fact of the matter remains: the addition of CCNU to a TMZ and radiation backbone appears to confer a significant survival benefit for all categories of patients, and particularly for subgroups known to have a worse outcome, that is, patients with glioblastoma, incomplete resection, and overexpression of O^6-DNA methylguanine-methyltransferase (MGMT).

The outcome of this study raises numerous questions. First, are the participants in the 2 studies similar? Looking at the characteristics of the patients, there is no difference in sex, age distribution, tumor location, histological subtype, or extent of resection between ACNS0126 and ACNS0423. Second, are these results specific to the pediatric population? A previous single arm adult study in newly diagnosed glioblastoma patients yielded promising results.[6,7] However, it seems that the significant toxicity observed with this combination prevented further development of this approach. In the pediatric setting, this combination is indeed more toxic than adjuvant treatment with TMZ alone. However, according to Jakacki et al, the toxicity was manageable, no toxic death was observed, and only 4 patients experienced neutropenic fever.

Where should we go next? The current use of adjuvant chemotherapy in pediatric patients with high-grade glioma relies on the results of a study conducted 40 years ago, which randomized 58 patients. This CCG-943 trial compared patients treated with radiotherapy alone (standard arm) versus radiotherapy plus lomustine, prednisone, and vincristine (PCV) chemotherapy (experimental arm). This trial showed that patients in the experimental arm had significant survival advantage (5 y event-free survival of 46% versus 18%).[8] The subsequent trial, CCG-945, failed to show a difference in survival between the 8-drugs-in-1-day chemotherapy compared with PCV.[4] For many, the results of this trial constituted indirect proof that chemotherapy had no role in the management of pediatric high-grade glioma. We have to keep in mind that both regimens, the so-called 8-drugs-in-1-day chemotherapy and the PCV, contained nitrosoureas, and

the results of ACSN0423 may shed new light on the interpretation of these results. This would suggest that, in the management of children with high-grade glioma, the best results thus far have been obtained with nitrosourea-containing regimens.

From a biological standpoint, there are some potential explanations for these results, in particular the spectacular difference in survival between the cohort of patients with MGMT-overexpressing tumors in ACNS0126 and ACNS0423. Although the results are surprising, there is a rationale to consider these 2 alkylating agents to be synergistic.[9] Despite similar mechanisms, TMZ is a monofunctional methylating agent resulting in persistent O^6-methylguanine DNA adducts, which in turn results in an aberrant DNA mismatch repair pathway, leading to double-stranded breaks and apoptosis. CCNU is a bifunctional chloroethylating agent whose action results in the formation of O^6-chloroethylguanine adducts that form lethal double-strand cross-links. The observation that survival is significantly improved in MGMT-overexpressing tumors with dual alkylator therapy may potentially be explained by MGMT depletion, due to an imbalance in the rate of DNA alkylation versus MGMT synthesis.[10]

A major challenge in interpreting this study is the lack of appropriate biological correlative studies. Specifically, the use of MGMT immunohistochemistry is controversial at best and completely unreliable at worst, particularly when DNA methods such as methylation-specific PCR and genome-wide methylation arrays are readily available and far more robust. As such, although the results for MGMT-overexpressing tumors are spectacular, this should be interpreted with a grain of salt. Interpretation of these results in the context of recently described methylation subgroups of pediatric glioblastoma, cytogenetic characteristics, and hotspot mutations (G34V, K27M) would be far more useful in identifying which patients are likely to benefit from this combined regimen.[11,12] Specifically, the significance of MGMT expression in predicting response to alkylating agents in pediatric high-grade glioma is unknown, as isocitrate dehydrogenase 1 mutations and a corresponding "cytosine–phosphate–guanine island methylated phenotype" subgroup are largely absent. Large cooperative groups such as the Children's Oncology Group need to acknowledge the importance of proper biological correlation in any future clinical trial.

One of the lessons from this trial concerns the methodology used in clinical trials for pediatric high-grade gliomas. While the number of pediatric patients with high-grade gliomas is far lower than in the adult population, therefore limiting the possibility to develop large clinical trials, it appears that the best methodology for these trials remains a randomized design. The recent successful completion of the HERBY study confirms the possibility to run such trials even in the case of an orphan disease.[13] Should cooperative groups consider this approach, they have no other choice but the branding of the ACNS0423 design as the "best standard of care."

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