Treatment of Glioma in the 21st Century: An Exciting Decade of Postsurgical Treatment Advances in the Molecular Era

Joon H. Uhm, MD, and Alyx B. Porter, MD

From the Department of Neurology and Division of Neuro-Oncology, Mayo Clinic, Rochester, MN (J.H.U.); and Department of Neurology, Mayo Clinic, Scottsdale, AZ (A.B.P.).

CME Activity

Target Audience: The target audience for *Mayo Clinic Proceedings* is primarily internal medicine physicians and other clinicians who wish to advance their current knowledge of clinical medicine and who wish to stay abreast of advances in medical research.

Statement of Need: General internists and primary care physicians must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. *Mayo Clinic Proceedings* aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

Accreditation: Mayo Clinic College of Medicine and Science is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Statement: Mayo Clinic College of Medicine and Science designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s).*™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

MOC Credit Statement: Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1 MOC point in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Learning Objectives: On completion of this article, you should be able to (1) identify molecular markers that play a role in the understanding of response to therapy in patients with high-grade glioma; (2) contrast the treatment options available and their efficacy in patients with high-grade glioma and various molecular signatures; and (3) recognize the larger clinical trials that have shaped the current management of high-grade glioma.

Disclosures: As a provider accredited by ACCME, Mayo Clinic College of Medicine and Science (Mayo School of Continuous Professional Development) must ensure balance, independence, objectivity, and scientific rigor in its educational activities. Course Director(s), Planning Committee members, Faculty, and all others who are in a position to control the content of this educational activity are required to disclose all relevant financial relationships with any commercial interest related to the subject matter of the educational activity. Safeguards against commercial bias have been put in place. Faculty also will disclose any off-label and/or investigational use of pharmaceuticals or instruments discussed in their presentation. Disclosure of this information will be published in course materials so that those participants in the activity may formulate their own judgments regarding the presentation.

In their editorial and administrative roles, William L. Lanier, Jr, MD, Terry L. Jopke, Kimberly D. Sankey, and Nicki M. Smith, MPA, have control of the content of this program but have no relevant financial relationship(s) with industry. Dr Uhm has received honoraria from Novocure, manufacturer of the Optune tumor-treating field device that is discussed in this article.

Method of Participation: In order to claim credit, participants must complete the following:

1. Read the activity.
2. Complete the online CME Test and Evaluation. Participants must achieve a score of 80% on the CME Test. One retake is allowed.

Visit www.mayoclinicproceedings.org, select CME, and then select CME articles to locate this article online to access the online process. On successful completion of the online test and evaluation, you can instantly download and print your certificate of credit.

Estimated Time: The estimated time to complete each article is approximately 1 hour.

Hardware/Software: PC or MAC with Internet access.

Date of Release: 6/1/2017

Expiration Date: 5/31/2019 (Credit can no longer be offered after it has passed the expiration date.)

Privacy Policy: http://www.mayoclinic.org/global/privacy.html

Questions? Contact dletcsupport@mayo.edu.

Abstract

The past decade has brought about major changes in the way we classify and have begun to approach patients with high-grade glioma. As we trend toward personalized medicine, we are now able to utilize the molecular characteristics of each individual's tumor in order to tailor their treatment, particularly if the patient is elderly or has a poor performance status at baseline. We address the state of the practice as of 2016 in regard to chemotherapy, immunotherapy, and tumor-treating fields. The goal of this review is to enhance readers' understanding of the nuances that are allowing clinicians to tailor the treatment of high-grade glioma more specifically.

 ■ Mayo Clin Proc. 2017;92(6):995-1004

The past decade has seen remarkable research advances in glioblastoma that have culminated in tremendous improvements in patient outcome, with extensions in overall survival that have never been seen previously. Whereas 2-year survival for patients with glioblastoma remained stagnant for decades at a dismal 10%, it nearly tripled to 27% with the advent of temozolomide (TMZ) and increased almost 5-fold for patients

whose tumors harbor a specific genetic alteration (O^6-methylguanine-DNA methyltransferase gene [*MGMT*] promoter methylation) in a pivotal study just over 10 years ago.[1-3] The publication of that pivotal study a decade ago was the beginning of one advance after another, each documenting improvements in survival for patients with gliomas. Through advances in the identification of molecular signatures found in these tumors, new directions have been identified that are guiding treatment options in the field. Such new directions include the key role of genetic alterations that will inevitably replace the standard diagnostic procedures based on microscopy (histology/grade). These genetic alterations help to better match specific treatment modalities with a tumor based on its biologic features. This article will highlight several key advances in chemotherapy that have occurred over the past decade that, in turn, direct us toward an even brighter future for our patients.

CHEMOTHERAPEUTIC EXTENSION OF SURVIVAL IN PATIENTS WITH GLIOBLASTOMA: TMZ AND THE IDENTIFICATION OF *MGMT* AS A MOLECULAR MARKER

As the field of neuro-oncology was approaching the end of the 20th century, we had amassed a wealth of information about the molecular biology of glioma cells, which, in turn, identified many potential targets for therapeutics. Figure 1 illustrates the signal transduction pathways that drive glioma growth, with several principal components: the growth factor receptor (GFR) at the cell surface functioning as a "docking station" for growth signals; secondary messenger systems within the cells that are activated by GFRs; the DNA as a common convergence point for many signal transduction pathways to activate expression of cancer-associated genes (oncogenes); and the protein products of those oncogenes that then define the malignant phenotype (cell cycle progression/mitosis, angiogenesis, tumor invasiveness).[1] Each component of this molecular diagram is an ongoing or potential target for therapeutics. Despite numerous drugs developed to inhibit the new molecular targets of signal transduction, in the end it was targeting DNA—the archetypal target in most cancers—that led to the first chemotherapy breakthrough with the advent of TMZ.[2,3]

The benefit of TMZ is summarized in Table 1. For decades, the dogma held that surgery[4] and radiotherapy (RT)[5] were the only 2 therapeutic modalities that improved survival of patients with glioblastoma multiforme (GBM), with only 10% of patients surviving 2 years. A pivotal European/Canadian study by Stupp et al[2] described the addition of a well-tolerated oral chemotherapeutic agent, TMZ, which alkylates DNA (adds methyl group—hence the term *alkylation*—to guanine residue of DNA) (since termed the *Stupp protocol*). The Stupp protocol includes TMZ at 75 mg/m^2 on days 1 through 42 with concomitant RT, followed by TMZ on days 1 through 5 of 28 for 6 consecutive months as adjuvant therapy at a dose of 150 to 200 mg/m^2. This regimen led to an improvement in 2-year survival to 27%. Furthermore, the presence of a specific alteration—methylation of the *MGMT* gene promoter—improved 2-year survival to 47%, a 5-fold increase compared with RT alone.[3] The *MGMT* gene product repairs the DNA modification caused by alkylators such as TMZ, and therefore, silencing of the *MGMT* gene by promoter methylation is thought to confer increased sensitivity to TMZ. As a result of these 2 back-to-back publications in 2005, RT combined with TMZ became the long-awaited new standard of care in newly diagnosed glioblastoma and *MGMT* the key molecular marker in our field.

TAILORING THE STUPP REGIMEN FOR THE ELDERLY PATIENT POPULATION

MGMT promoter methylation thus became an important prognostic marker in neuro-oncology. Given that the benefit of TMZ is most apparent when this gene alteration is present, *MGMT* methylation may also be a marker that guides therapy choices. The role of *MGMT* in helping to guide therapy was highlighted in a series of reports pertaining to optimization of treatment for the elderly population with high-grade glioma.

Table 2 summarizes the evolution of treatment—in particular, the trimming of the Stupp regimen—for the elderly patient population. The French study[6] found that a standard 6-week course of RT (6000 cGy over 6 weeks) improves survival compared with palliative care alone. However, the standard RT course was poorly tolerated by

Mayo Clin Proc. ■ June 2017;92(6):995-1004 ■ http://dx.doi.org/10.1016/j.mayocp.2017.01.010
www.mayoclinicproceedings.org