ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Recent and Ongoing Clinical Trials in Glioblastoma

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H&O How common is glioblastoma, and what are the symptoms?

GL Glioblastoma is the most frequent glioma, and it accounts for the majority of malignant primary brain tumors. The incidence is approximately 6 to 10 per 100,000 people/year. Glioblastomas account for approximately 50% of gliomas in all age groups. The incidence peaks among people ages 55 to 60 years. Glioblastoma is more common in men than women. The 2016 classification from the World Health Organization divides glioblastomas into categories of primary and secondary based on the presence of a mutation in the isocitrate dehydrogenase (*IDH*) 1 or 2 gene. Primary glioblastoma refers to patients with the *IDH* wild-type gene. Secondary glioblastoma refers to patients with the *IDH* mutation.

Patients with glioblastoma may have different signs and symptoms based on the direct and indirect effects of the tumor. Approximately 40% to 60% of patients have a focal neurologic deficit. About 30% to 60% of patients experience headaches, owing to increased intracranial pressure. In approximately 20% to 40% of patients, seizures are the first sign of a glioblastoma. Some patients may exhibit a change in personality.

H&O What is the prognosis?

GL Overall, the survival of patients with glioblastoma is still poor. The median overall survival is approximately 15 months, with a 2-year survival rate of 30%. An important factor for prognosis is the methylation status of the O^6-methylguanine DNA methyltransferase (*MGMT*) gene. Patients with this methylation have a better prognosis. A better prognosis is also seen in patients with secondary glioblastoma, who have the *IDH* mutation.

> In recent years, the maintenance of an acceptable quality of life has become a goal of patient-centered neuro-oncologic treatment approaches.

Virtually all patients develop relapsed disease. After diagnosis, the median time to recurrent disease is approximately 5 to 8 months. In approximately 5% of patients, however, survival will be 5 years or longer.

H&O What is known about the biology of glioblastoma?

GL In general, glioblastoma is a vascularized tumor with high expression of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), with the

ensuing attachment to its VEGF receptor 2 localized to endothelial cells. In younger patients with glioblastoma, the *IDH* mutation is often the first hallmark alteration identifying so-called secondary glioblastoma. Other gene mutations in this setting are found in alpha thalassemia/mental retardation syndrome X-linked (*ATRX*) and *TP53*. There may also be a mutation or loss of retinoblastoma protein and the phosphatase and tensin homolog (*PTEN*) gene.

For primary glioblastoma, the hallmark alteration consists of a mutation or amplification in the epidermal growth factor receptor (*EGFR*) gene. Other alterations include the p16 deletion, loss of heterozygosity of chromosome 10q, and the *TERT* promoter mutation.

H&O Are there any recent insights into the genetics of glioblastoma?

GL Based on new research into genetic mutations, glioblastomas can be divided into 3 classes: proneural tumors, mesenchymal tumors, and the classical glioblastomas. Another important insight into the genetics of glioblastoma is the identification of diffusion transcripts, such as the fibroblast growth factor receptor 3 (*FGFR3*) and transforming acidic coiled-coil containing (*TACC*) gene fusion, which are seen in about 3% to 5% of patients. Importantly, these alterations could be clinically actionable with the new drugs.

H&O What is the traditional treatment approach for glioblastoma, and how effective is it?

GL The traditional treatment approach for glioblastoma consists of maximal safe resection followed by adjuvant treatment with radiation therapy at 60 Gy in association with temozolomide. One month after the completion of the combination therapy, the patient begins treatment with at least 6 cycles of temozolomide. This approach is not very effective. Only 30% of patients are alive 2 years after diagnosis, and 5% are alive 5 years from diagnosis.

H&O Do older patients require modified regimens?

GL Patients ages 70 years or older can require modified regimens consisting of hyperfractionated radiotherapy at 40 Gy in combination with temozolomide. Treatment is followed by 6 or 12 cycles of maintenance temozolomide. As shown in a recent trial by Perry and colleagues, this approach is the most effective one for elderly patients, especially those with methylated *MGMT*. However, quality of life is a particular concern when selecting treatment for elderly patients. These patients require evaluation with comprehensive geriatric assessment (CGA) for quality of life, comorbidities, and neurocognitive functions. CGA is needed for improving treatment decisions and outcomes in elderly patients with glioblastoma.

H&O What are the quality-of-life issues faced by patients with glioblastoma?

GL Glioblastoma patients have a poor survival of approximately 15 months. Therefore, maintenance of a good quality of life becomes even more important than survival. Patients can develop neurologic deficits, motor deficits, and anxiety. Among patients with newly diagnosed glioblastoma, quality of life can be diminished by the standard treatments, including surgery, radiation therapy, and chemotherapy, as well as supportive medications, such as corticosteroids and antiepileptic drugs. In recent years, the maintenance of an acceptable quality of life has become a goal of patient-centered neuro-oncologic treatment approaches. Quality of life is now an outcome measure in most clinical trials. Moreover, in our center at the Veneto Institute of Oncology, we have a psychologist who specializes in ways to increase quality of life among our neuro-oncology patients.

H&O What factors have limited the development of new treatments for patients with glioblastoma?

GL The major factor limiting the development of new treatments is the blood-brain barrier, which many drugs cannot cross. The result is a low concentration of the drug in glioblastoma cells. Another factor is that immunotherapy can cause brain damage, specifically edema. This important toxicity has limited the development of immunotherapy in glioblastoma. Moreover, with regard to immunotherapy, glioblastoma is considered a "cold tumor," which could be an important reason for the poor efficacy of this therapy.

H&O What are the findings of recent clinical trials?

GL The REGOMA trial (Regorafenib in Relapsed Glioblastoma) is an Italian, multicenter, randomized phase 2 study analyzing the activity of regorafenib (Stivarga, Bayer), coordinated by Veneto Institute of Oncology. Regorafenib is an oral multikinase inhibitor. This trial evaluated regorafenib in relapsed glioblastoma among patients previously treated with radiation therapy and temozolomide (known as the Stupp protocol). Results, presented at the 2017 European Society for Medical Oncology (ESMO) meeting, showed that regorafenib

had significant activity, including a longer overall survival compared with standard treatment with lomustine. Updated results were presented at the 2018 American Society of Clinical Oncology (ASCO) meeting. This is the first randomized, comparative trial demonstrating efficacy and safety of an antiangiogenic drug in recurrent glioblastoma.

The phase 3 CheckMate-143 trial compared immunotherapy with nivolumab (Opdivo, Bristol-Myers Squibb) vs bevacizumab (Avastin, Genentech) in patients with relapsed glioblastoma. Results were presented at the 2017 European Association of Neuro-Oncology congress. Unfortunately, this study did not show that nivolumab was superior to bevacizumab in terms of progression-free survival or overall survival. Approximately 8% of patients did respond, and the researchers are analyzing whether any biomarkers can be used to select who is most likely to benefit from immunotherapy.

H&O Are there any biomarkers currently in use?

GL Methylation of *MGMT* is an established predictor of temozolomide efficacy. There are no new biomarkers that can predict efficacy. Antiangiogenic treatment has demonstrated no efficacy as first-line or second-line treatment in glioblastoma. A small group of patients responded to this treatment, but no predictive biomarker was found.

For immunotherapy, research in other types of malignancies, such as colorectal cancer, lung cancer, and breast cancer, has shown that the presence of microsatellite instability or high "tumor mutation load" could predict efficacy. However, we have to find biomarkers for glioblastoma patients.

H&O Are any novel agents under investigation?

GL An important agent under investigation is the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib (Lynparza, AstraZeneca). Small studies have suggested that this new drug may have activity against glioblastoma cells. A larger prospective study is currently in development. Another interesting agent is depatuxizumab mafodotin. This antibody drug conjugate delivers a microtubule toxin payload to an antibody against EGFR. Trials are investigating depatuxizumab mafodotin as first-line or second-line therapy in combination with temozolomide or as monotherapy.

Immunotherapy is under investigation as first-line or second-line treatment in glioblastoma patients. In particular, ongoing trials are evaluating nivolumab in these settings. At the Veneto Institute of Oncology, we are evaluating pembrolizumab (Keytruda, Merck), another immunotherapy drug, in recurrent glioblastoma patients with microsatellite instability.

H&O Will newer treatments be used in combination with other modalities?

GL The newer treatments might be used in combination with standard treatments. For example, a small study found that radiation therapy could improve the efficacy of immunotherapy. A treatment regimen might consist of radiation therapy followed by immunotherapy. Immunotherapy might also be used with antiangiogenic treatment, which could increase the immunotherapy drug concentration within the glioblastoma cell.

Moreover, as seen with other tumors, it may be possible to combine 2 or 3 immunotherapeutic drugs with different mechanisms of action. Another modality that might be used in combination with other new or established treatments is tumor-treating fields, a therapy that uses electric fields to inhibit mitosis via transducer arrays applied to the scalp.

H&O Are there any other ongoing trials?

GL Based on the promising results seen with regorafenib in the phase 2 REGOMA trial, a phase 3 study will start shortly. This international trial will evaluate the efficacy and safety of regorafenib in recurrent glioblastoma. Two ongoing phase 3 trials, CheckMate-498 and CheckMate-548, are evaluating nivolumab combined with radiation therapy, with or without temozolomide, as first-line treatment in glioblastoma. As mentioned, the CheckMate-143 trial found that nivolumab did not improve outcome in the second-line setting. It is hoped that more efficacy will be found in the first-line setting.

Shortly, a trial from the European Organisation for Research and Treatment of Cancer (EORTC) evaluating the efficacy of marizomib, a proteasome inhibitor, in patients with newly diagnosed glioblastoma will start at the Veneto Institute of Oncology.

H&O Does the development of drugs for glioblastoma have implications for other types of cancers?

GL Glioblastoma is very different from other types of tumors, so it is difficult to say whether developments will have additional implications. The only characteristic that might have implications for other tumors is that the field provides numerous examples of drugs that fail to cross the blood-brain barrier. These findings could be important for the treatment of brain metastases in lung cancer, breast cancer, and other malignancies.

Disclosure

Dr Lombardi has no real or apparent conflicts of interest to report.

Suggested Readings

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