

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Barriers to the Development of Drugs for Primary Brain Tumors



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H&O What are the most common types of primary brain tumors?

SC The most common types are meningioma, tumors that arise in the lining of the brain, and glioma, tumors that are inherent to the normal cells within the brain parenchyma. Prognosis for glioma patients varies according to many different factors, such as the patient's age and clinical status, the cell subtype, the tumor grade, and the molecular and genetic characteristics. Gliomas, especially the invasive types, universally recur. The median survival for adults with the most common primary malignant tumors—grade IV astrocytoma or glioblastoma—is approximately 15 to 20 months.

H&O What types of treatments are available?

SC The first step in treatment is maximal safe resection, which is usually followed by radiation and chemotherapy. For glioblastoma in adults, the effectiveness is limited by the tumor location, and whether resection would be safe. These tumors are invasive and infiltrate into the normal tissue. Removing normal tissue from the brain could affect the patient's neurologic and cognitive functioning. Surgery and radiation are focal treatments that reach the tumor directly. High doses of radiation are limited by adverse events. Chemotherapy with alkylating agents has been used in glioblastoma. The effectiveness can depend on some of the markers that are now being found within these tumors. In glioblastoma, the biologic pathways are dysregulated, so there may be an opportunity to use targeted treatments. Another treatment is alternating electric

field therapy, which has shown some evidence of survival benefit.

H&O What are the unmet needs in the management of brain tumors?

SC Advances in surgery, radiation, and drug development have not significantly increased survival for these patients, so the development of more effective treatments is a major priority. It is also important to improve how patients tolerate treatment and to decrease side effects and address quality-of-life issues, particularly cognitive function.

Another important unmet need is caring for caregivers. Patients with brain tumors exhibit not only physical changes, but also emotional and cognitive changes. It can be difficult for patients to continue to work and to function in their usual capacity at home. Caregivers assume a lot of responsibility for the patient's care.

H&O What are the challenges in developing drugs for brain tumors?

SC The challenges are substantial and multifactorial, as evident by the paucity of effective agents and the high number of negative phase 3 trials conducted in glioblastoma. Brain tumors are a heterogeneous disease. By the time of diagnosis, a patient has multiple clones and dysregulated pathways. It is difficult to target specific mechanisms. A better understanding of tumor biology is necessary for drug development.

Effective drug delivery is another challenge. Efficacy against brain tumor cells in a petri dish or in animal

models may not translate into clinical benefit. In patients, drugs must cross the blood-brain barrier and penetrate into the brain parenchyma at high enough concentrations within the tumor environment to have a therapeutic effect. Assessment of drug delivery and drug distribution within the brain is important.

Patients with brain tumors are prone to seizures, headaches, and other neurologic changes. Therefore, a major concern with any new drug being tested for brain tumors is whether it will cause neurologic symptoms.

Drug resistance mechanisms and tumor evolution are other important factors. A tumor's molecular and genetic makeup at diagnosis will change after treatment. A treatment that is effective at the time of initial diagnosis may no longer be effective after progression or recurrence.

Another challenging aspect is how to identify drugs with a potential for benefit. Robust preclinical models that recapitulate human disease can be used to establish scientific rationale for moving an agent to clinical testing. Early, accurate assessment of drug efficacy, in conjunction with tissue analysis and imaging, can assist with later-phase development of agents that are likely to demonstrate success. It will also be helpful to identify predictive biomarkers that will allow better selection of treatment for particular patients.

In addition, a large barrier is the time, cost, and effort of activating and conducting trials. The incidence of glioma is relatively low, at less than 20,000 cases per year in the United States. Large studies must therefore be collaborations across institutions. In addition, the low incidence means that this field may not be a priority for the pharmaceutical industry.

H&O What are some unique aspects to clinical trials in brain tumors?

SC Many trials require tissue samples, and sometimes there are specifications regarding the amount of tissue and how it is prepared. This is a challenge because, depending on where in the brain the tumor is located, it may not be possible to obtain large tissue samples. In addition, some treatments are delivered directly into the brain and require adequate tumor size and a suitable location. Such specific enrollment criteria can exclude many patients.

There is a high potential for drug-drug interactions because many patients are receiving therapy for symptoms, such as corticosteroids to treat brain edema, anticonvulsants for seizures, and anticoagulants for thromboembolic disease.

Insights into the tumors' biology is also challenging traditional clinical trial design. A glioblastoma that arose from a grade 2 or 3 tumor has different mutations and biology than a tumor that did not. Glioblastoma is

not just one type of tumor, and it can be challenging to encompass the different types in clinical trials. The World Health Organization (WHO) has recently changed its classification of glioblastomas and gliomas. The WHO criteria incorporate not only the histologic pathology, such as the type and shape of cells, but also the molecular and cytogenetic mutational status within the tumors. It is challenging to compare new data with data from historical controls because of the different classification criteria used in the past.

Phase 0 trials, which assess drug penetration and target modulation, are important because they can help inform the design for subsequent phase trials. Phase 0 trials can employ pharmacogenetics, pharmacodynamics,

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and metabolic imaging to determine a drug's effect in a patient who receives a new therapy and then undergoes surgery. Phase 1 trials evaluate toxicity, determine the maximum tolerated dose, and assess correlative imaging and tissue endpoints. Phase 2 trials identify signals for efficacy, provide more data on the utility of imaging and tissue endpoints, and can recognize potential predictive markers. Phase 2 trials should also assess quality of life. Phase 3 trials usually compare a new treatment against the standard of care, and evaluate overall survival and quality of life. Phase 3 trials can also validate imaging and tissue endpoints, which can then inform subsequent care.

H&O What are the weaknesses associated with the current clinical trial endpoints?

SC Overall survival is the most robust endpoint, but it is associated with several limitations. In the newly diagnosed setting, there is always a question of whether overall survival can be confounded by treatment at progression. In some uncommon brain tumors, such as oligodendroglioma, the median survival is decades. For these patients, correlative endpoints, such as progression-free survival and overall response rate, need to be validated as surrogates for survival.

Assessment of progression-free survival and overall response rely on imaging assessment. It can be difficult

to accurately define the imaging changes in the posttreatment setting. The terms *pseudoprogression* and *pseudoreponse* illustrate this ambiguity. Accurate assessment of tumor burden is a focus of much research.

Another concern with study endpoints is that progression-free survival or objective response may not translate into improved overall survival. Quality of life may be another way to assess benefit. Assessment, however, requires prospective trials and validated, serial measurements, which could be limited by patient dropout.

Many therapies with positive phase 2 data fail to achieve a benefit in phase 3 trials. Single-arm studies can be confounded by prognostic factors. One example is age; if a phase 2 trial primarily enrolls younger patients, benefits may not be seen in a phase 3 trial with a broader population.

H&O How is imaging used to assess tumor response?

SC Contrast-enhanced or gadolinium-enhanced magnetic resonance imaging (MRI) scans are typically used to determine whether the tumor is responding to treatment or enlarging. Imaging can show the tumor's location and impact on the normal structures within the brain. Gadolinium can also assess the integrity of the blood-brain barrier.

Clinical decisions rely on an accurate assessment of disease. Imaging is limited in terms of providing information about the cellular makeup within the brain. Radiation or chemotherapy can change brain tissue and break down the blood-brain barrier. I am a member of the executive committee of the Response Assessment in Neuro-Oncology (RANO) working group, which was started in 2008 to improve the use of imaging. Clinicians were recognizing effects seen from treatment that did not correspond with the classic understanding of what happens when a tumor improves or progresses. The use of bevacizumab (Avastin, Genentech) raised this issue. Within 24 hours of administration, bevacizumab was associated with dramatic improvements in contrast enhancement, which would classically correlate to improvements in the tumor. Physicians knew, however, that tumor response in this manner was not expected. Bevacizumab is effective at reconstituting the blood-brain barrier, making it more difficult for the gadolinium to leak into the brain tissue. It was not surprising therefore that the improvements in response rate and progression-free survival seen with bevacizumab may not lead to an increase in overall survival.

As a corollary, contrast enhancement that worsened after treatment was thought to indicate progressive disease. However, a scan repeated a month later without a change in treatment might show improvement. These

tumors do not regress spontaneously, so we recognized that apparent worsening on an MRI does not necessarily indicate tumor progression. We therefore had to reassess the use of imaging criteria.

The RANO effort recognized that criteria must be tailored not only to the specific type of tumor but also to the nature of the treatment. Immunotherapy is a good example. The idea behind immunotherapy is to boost the immune system, and that could lead to an increased inflammatory response. If the immunotherapy is successful, and the immune cells infiltrate the tumor, that might translate into transient inflammatory changes that could resemble tumor progression on an MRI scan. This effect must be accounted for in the imaging criteria. The Immunotherapy RANO (i-RANO) group has generated information about how to integrate this effect into clinical trial design.

H&O How can tumor quantification be improved?

SC The RANO group studied not only how to standardize imaging but also how to improve tumor quantification. Metabolic imaging has become an important component of assessment, and incorporates the use of position emission tomography, as well as advanced biologic and physiologic imaging.

MRIs assess structure. The goal, however, is to go beyond structure and evaluate biology, metabolism, and chemical makeup of the tissues. Modalities under investigation include spectroscopy, which detects chemical pat-

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terns within the brain tissue. One of our research efforts includes image-guided biopsies to measure tumor burden and differentiate the tumor from the treatment effect. With this approach, patients undergo multiparametric and spectroscopic imaging before surgery to characterize the tumor and identify areas within the tumor that are biologically distinct. The surgeon samples those areas before resection of the tumor. Then we can correlate that

information to the imaging, to obtain a spatial dimension of where the tumor is located in the brain and to identify molecular, cytogenetic, and histopathologic features. This approach provides a robust dataset to validate the imaging characteristics that could serve as surrogates for tumor biology.

It is necessary to identify noninvasive characteristics of tumors that can better drive decision-making. We are using spectroscopic imaging to identify biomarkers of malignant transformation of low-grade glioma. This approach is important, not only to guide surgeons to the most aggressive area of the tumor, but also when planning clinical trials so that the biology of the tumor can be used to assign patients to the correct treatment arms.

A novel approach to the noninvasive measure of tumor burden and response is with hyperpolarized carbon-13. Hyperpolarization with carbon-13 provides a signal-to-noise ratio of more than 10,000-fold, meaning that the molecules can be more easily detected with current technology. The hope is that use of imaging and hyperpolarization will allow us to noninvasively evaluate, in real-time, whether a drug reaches a tumor and if it has an effect. Imaging the patient before the drug is administered and then immediately afterward should be able to identify a signal of the drug's effect. This is a classic example of how imaging can be used to determine treatment response. We want to correlate this information to endpoints such as progression-free survival and overall survival.

H&O Are there any recent insights into brain tumors that might lead to new treatments?

SC Molecular cytogenetic characterization of tumors is an exciting area. Ongoing studies are evaluating the importance of the isocitrate dehydrogenase (*IDH*) mutation, not only as an early marker of tumor development but as a potential target for treatment. Approximately 80% of patients with glioblastoma have the telomerase reverse transcriptase (*TERT*) promoter mutation, which allows for regeneration of telomeres. The *TERT* promoter mutation is found only in the tumor and not normal tissue, which is unique. Targeting of long, noncoding RNA is another promising treatment.

There are many studies of immunotherapy approaches that include checkpoint inhibitors, vaccines, and chimeric antigen receptor T-cell therapy. Many of the tumor types have multiple pathways that are abnormal. It is necessary to determine which pathway is the most important and how many should be targeted. We need to identify the mechanisms behind drug resistance and tumor evolution.

Several methods of drug delivery are under investigation. Convection-enhanced delivery employs a catheter and a pressure gradient to force agents directly into the brain, as opposed to classic diffusion across a concentration gradient. Oncolytic viral therapy can be used to deliver agents or genes that can confer cytotoxicity of a prodrug. Nanotechnology will allow a drug to be administered into the brain tissue itself.

H&O How is your institution addressing the needs of caregivers?

SC Addressing the needs of caregivers is an important way to maximize the benefit of interventions for these patients. The caregivers are often responsible for administering the medications, and they must be aware of how to manage adverse events. In addition, declines in the patient's cognitive function may increase the caregiver's responsibilities in the home.

Three years ago, the University of California, San Francisco (UCSF) developed a unique caregiver program. The UCSF Neuro-Oncology Gordon Murray Caregiver Program supports families and caregivers of adult UCSF patients with a primary brain tumor. The purpose of the program is to improve the quality of life of the caregivers and the patients by providing education, information, and referral to community resources. The program also offers individual counseling, a caregiver support group, a peer caregiver program, and educational opportunities. More information about the program can be found at the following link: www.ucsfhealth.org/programs/neuro-oncology_caregiver_program/.

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Suggested Readings

Butowski N, Chang SM. Endpoints for clinical trials and revised assessment in neuro-oncology. *Curr Opin Neurol*. 2012;25(6):780-785.

Chang SM, Wen PY, Vogelbaum MA, Macdonald DR, van den Bent MJ. Response Assessment in Neuro-Oncology (RANO): more than imaging criteria for malignant glioma. *Neurooncol Pract*. 2015;2(4):205-209.

Lin NU, Lee EQ, Aoyama H, et al; Response Assessment in Neuro-Oncology (RANO) group. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol*. 2015;16(6):e270-e278.

Okada H, Weller M, Huang R, et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. *Lancet Oncol*. 2015;16(15):e534-e542.

Page MS, Chang SM. Creating a caregiver program in neuro-oncology [published online August 26, 2016]. *Neurooncol Pract*. 2016. doi:10.1093/nop/npw019.