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A Look at Current & Potential Therapies for High Grade Glioma

Announcer:
You're listening to ReachMD. Welcome to this medical industry feature, titled "A Look at Current & Potential Therapies for High Grade Glioma" sponsored by Tocagen. The following speakers have received compensation from Tocagen.

Here's your host, Dr. Jenn Simmons.

Dr. Simmons:
Tumors of the brain are different from other tumors found in the body they have their own unique grading system based on specific features of cancer growth. Among the most aggressive brain tumors are high grade gliomas, and it's the recognition and multi-disciplinary management of the treatment of these cancers that will become the focus of today's panel.

From the ReachMD studios in Fort Washington, Pennsylvania, I'm Dr. Jenn Simmons, and joining me to explore current insights for the treatment and management of patients with high grade gliomas are Dr. Clark Chen, Professor of NeuroSurgery at the University of Minnesota Medical Center; Dr. Christina Tsien, Professor of Radiation Oncology at the Washington University School of Medicine; and Dr. David Piccioni, Director of Clinical Neuro-Oncology at the University of California San Diego Moores

Cancer Center.

Thank you all for joining me today!

Dr. Simmons:
What are the main types of brain tumors, and how do they generally differ from each other with respect to prognosis?

Dr. Piccioni:
There is actually more than 120 different types of tumors of the brain and the central nervous system. For most brain tumors, these tumors start in the brain and stay in the brain. And so while they can spread within the brain or even in the rest of the central nervous system, other places, say in the brain or the spine, they aren't tumors that go outside the central nervous system. In the WHO Grading System, there's actually four different grades of tumors, grade I to IV.

So grade I tumors are very slow-growing tumors, and these are tumors that are often cured by surgical resection. Grade II tumors these are where tumors really start to have infiltrating features. Grade III tumors usually have what we call pleomorphism. They are more angular, they look slightly different, and you can tell that there is a difference between kind of regular cells in the brain and these other cells under the microscope. So that brings us to grade IV. They usually have vascular proliferation, and then sometimes these tumors are growing so quickly that the center of them actually dies off a little bit and you can get some necrosis or actually get some areas of dead tissue. And these are surely the most fast-growing tumors that can really grow quickly and spread quickly.

So usually, the tumors with the lower grades have better overall survival. The tumor type in the gliomas with the best survival is the pilocytic astrocytoma. This is a tumor that is a grade I tumor that is not infiltrating into the rest of the brain and like most grade I tumors, can usually be treated with surgery alone and has an excellent long-term prognosis. Next, are the oligodendrogliomas, who with the proper treatment, tend to do the best of the infiltrating gliomas, which are the gliomas between grades II and grade IV, followed by the astrocytomas. And then as the tumors get anaplastic features, which is another word sort of synonymous with grade III tumors, the survival decreases a little bit, and then finally the tumor with the worst prognosis is glioblastoma, which is really just another word for a grade IV astrocytoma. And these are the sort of most aggressive tumors in the brain. So we use the phrase high grade glioma to refer to tumors that are grade III or grade IV tumors.

High grade gliomas are tumors that we have treatments for, but we don't necessarily have cures for. These tumors are all infiltrative and so while surgery can remove the bulk of the tumor, we want to just try to get out as much of the tumor as we can without affecting the person's function. And so with all

these tumors, we want to treat them with surgery to get the bulk of the disease out as possible, and then try to come up with some treatment to treat the remaining part as well, and so that's usually a combination of radiation and chemotherapy. And when tumors come back in the recurrent setting, we have other targeted drugs like bevacizumab, to try to treat these tumors. But because none of these treatments are cures, we are looking into new and novel treatments and testing things with clinical trials to try to improve the outcome for these patients.

Dr. Simmons:
What makes high grade glioma unique and so difficult to treat?

Dr. Chen:
There are several factors that render high grade glioma one of the most difficult cancers that we face as physicians. The first is that high grade glioma resides within the brain and there is a barrier called a blood brain barrier, which prevents toxins from entering the brain. And unfortunately, our body treats many chemotherapies like they're toxins, and so most chemotherapies actually do not get into the brain effectively. Consequently, our therapeutic options are very limited. Additionally, high grade gliomas are extremely infiltrative, that is they're microscopic tumors and tentacles of tumors that extend throughout the brain, even if only a small portion of that can be visualized on the MRI. So, it is very difficult, if not impossible, to remove every bit of the tumor. The third issue is that high grade gliomas are intrinsically very resistant to chemotherapies and to radiation therapy. And, finally, as we understand more and more about high grade gliomas, we've come to appreciate that high grade gliomas do not consist of a single type of cell. There are differences in subsets of cancer cells that are found in the same patient, and more complicated than that are that normal cells are meant to fight tumors are being recruited into the tumor to facilitate its growth, and so because of the significant heterogeneity, it's very, very difficult to target this tumor.

Dr. Simmons:
Are there any known causes or risk factors for gliomas, and can they be avoided?

Dr. Tsien:
In the majority of patients, there is really no specific cause for gliomas. Certain families may have germline gene alterations that are associated with DNA that lead to an increased risk of gliomas. Prior radiation exposure can also be related to an increased risk of gliomas. The common forms of radiation that we worry about in our everyday lives, including electromagnetic fields from whether its powerlines or microwave ovens or being on airplanes, those have not shown an increased risk of gliomas. It's unclear at this time whether cell phone use increases the risk of brain cancer.

Dr. Simmons:

What is the standard of care for newly diagnosed high grade glioma?

Dr. Chen:
Because of the aggressive nature of this disease, the standard of care treatment involves maximal resection, followed by concurrent chemotherapy and radiation therapy.

Dr. Simmons:
Are there specific biomarkers that would influence prognosis?

Dr. Piccioni:
As we've learned more about the molecular features of these tumors, we've found that there are biomarkers that really can help us determine if the prognosis is better or worse, based on different features. So for the lower grade gliomas, especially the grade II and grade III astrocytomas and oligodendrogliomas, one of the most important biomarkers is really the IDH mutation. This mutation actually infers a survival advantage compared to those tumors that don't have it.

For the glioblastomas, there was another marker, MGMT, which helps predict whether tumors would respond well to the temozolomide chemotherapy or not. And so that's something else that can help play into the overall prognosis aside from just the histologic grade and really start to use those molecular features to give us some additional information.

Dr. Simmons:
Why have there been so few new treatments for high grade glioma patients in the last 15 years?

Dr. Piccioni:
There've been numerous studies over the last twenty years to really try to identify new treatments, validate novel targets, and try to improve our overall standard of care for these patients. You know, one of the main areas that we looked into for many years was really targeted therapy. They've worked well in the preclinical setting, but really have kind of failed when we've moved on to larger randomized phase 3 clinical trials. And there's lot of different factors that may influence why that was the case and why the brain cancer experience has really been different from say, the lung cancer experience. So, one of the main factors responsible for failure of these drugs to improve overall survival is really the inability of treatments to cross the blood brain barrier. Sometimes, we also have the emergence of resistance pathways. So, even if you do have, a drug and it actually does get through the blood brain barrier and does what the drug is supposed to do, you often get a parallel pathway that gets activated through some sort of other mutation or alteration that now has resistance to your drug and signaling through a separate pathway that can then stimulate tumor growth.

The third thing that is problematic for targeted therapies has to do with intratumoral heterogeneity. If

you use a targeted therapy that's only going after one mutation or one pathway, that might be effective for that subpopulation of tumor cells that has that mutation, but then there are other parts that don't have that mutation and they can continue to grow.

Another factor has to do with the definition of clinical endpoints. What really took us a while to understand was the concept of pseudoprogression. When your therapy is actually working, the tumor kind of looks bigger on the scan. There may be more uptake of the contrast enhancement on the MRI. There might be more swelling or edema, where things actually look worse, and we need to incorporate that into our clinical trial design and really have ways to try to evaluate is this tumor actually growing or is it actually responding to the treatment and not abandon these new treatments in these new clinical trials early for things that just look worse on the MRI scan.

Lastly, so it's very hard to get tissue to be able to evaluate before and after different treatments to learn things about why that treatment worked or didn't work. Brain surgeries are much more involved, and even to get a simple biopsy requires a much bigger procedure and operation and so we don't always get the tissue in these clinical trials to figure out what went wrong and how we can improve on things in the future.

Dr. Simmons:
For those just tuning in, you're listening to ReachMD, and I'm Dr. Jenn Simmons. Here with me today are Drs. Clark Chen, Christina Tsien, and David Piccioni to talk about high grade gliomas.

Without any major therapeutic advancements in glioma, are there ways to improve outcomes with our current treatment approaches?

Dr. Chen:
Yes. We can improve the outcome of our patients by working more closely together in a team setting involving radiation oncologists, neuro-oncologists, and neurosurgeons. We and others have published results demonstrating that the survival of high grade glioma patients have indeed improved over the past three decades. The improvement is modest, but there is genuine improvement in terms of survival, and we attribute that improvement to the establishment of multidisciplinary boards, where we make decisions in terms of clinical care together as a team.

Dr. Simmons:
Dr. Tsien, would you like to add anything to that?

Dr. Tsien:
A multidisciplinary team approach is really essential to improving outcomes. The ability of a multidisciplinary specialty, including radiation therapy, neurosurgeons, and neuro-oncologist to work

together to design the most innovative clinical trials and having clinical trial enrollment is really important.

Dr. Simmons:
Are there unique aspects to the clinical care of recurrent high grade glioma patients?

Dr. Chen:
Yes. The care of recurrent high grade glioma patients is particularly challenging because there is currently no standard of care. In the absence of a prescriptive optimal treatment paradigm, it is essential that we solicit input from a broad spectrum of intellectual disciplines, including neuro-oncology, neuroradiology, neurosurgery, and radiation oncology.

Dr. Simmons:
What is the latest thinking around the value of resection in recurrent disease?

Dr. Chen:
Traditionally, surgical resection is of benefit in patients who are symptomatic in the recurrent setting. Additionally, resection ascertainment of clinical specimens may be required for participation in select clinical trials. The controversy in terms of resection in the recurrent setting is, does it improve survival? There are select studies that demonstrate improved survival if a patient were to undergo total resection in the recurrent setting, but the jury is still out.

Dr. Simmons:
Looking ahead, what do you think are the most promising new therapies on the horizon?

Dr. Piccioni:
Well, certainly, this has been a very difficult disease to treat and we've always wanted to do something to improve patient outcomes and overall survival. And really, I think we want to try to keep our options at this point and look at a whole bunch of different therapeutic options to try to figure out what the next best step might be. We want to look at new targets. We want to look at better blood brain barrier penetration. We want to look at immune therapy, and we want to look at combination therapies. And I think the key to beating this difficult disease is really going to be along those paths.

Dr. Simmons:
Dr. Chen, what are your thoughts on that?

Dr. Chen:
Because we understand that highgrade gliomas consist of many different types of cells within the same tumor mass, whatever therapy we develop that's going to be effective has to be able to attack that

problem. It has to be able to destroy multiple different types of tumor cells in a single setting. And in that context, immunotherapy is very attractive. We could teach it to attack different types of tumor cells and yield meaningful improvement in the outcomes of our patients and their qualities of life.

Dr. Simmons:
Well on that note of promising options on the horizon for this devastating disease, and I want to thank you all for your insights today. Doctors, great to have you on the program!

I'm Dr. Jenn Simmons. Thanks for joining us.

Announcer:
This program was sponsored by Tocagen. If you missed any part of this discussion, visit ReachMD.com/highgradeglioma. This is ReachMD. Be part of the knowledge.