Enrolling Glioma Clinical Trials with Dr. Stephen Bagley

Melanie Cole, MS (Host): Welcome to the podcast series from the specialists at Penn Medicine. I'm Melanie Cole. And joining me today to highlight Penn-led clinical trials for glioma is Dr. Stephen Bagley. He's an Assistant Professor of Medicine and Hematology-Oncology at the Hospital of the University of Pennsylvania.

Dr. Bagley, it's a pleasure to have you join us as we get into these fascinating trials. Start by telling us a little bit about the trend in current diagnosis of glioma.

Stephen Bagley, MD: Thanks, Melanie, and it's a pleasure to be here to talk about these exciting studies. So right now, in the world of glioma, a lot's changed just in the last few years. The World Health Organization actually revamped the classification system for central nervous system tumors in 2021. And since then, we rely much more on molecular diagnostics than we ever have before to form an integrated diagnosis for each patient.

So, this integrated diagnosis combines elements of the histopathology or traditional grading for gliomas with molecular features. And one of the diseases that's been most impacted by this has been glioblastoma, where there are certain subtypes of glioblastoma that we would have used to call, you know, a grade 3 tumor. But now, based on certain molecular features, these tumors can also be lumped into the category of grade 4 glioblastoma, and therefore are actually eligible for many of the glioblastoma clinical trials.

Host: Well, thank you for that. So, looking at the current treatment landscape for gliomas, what options are available as of right now?

Stephen Bagley, MD: So, for a new patient with a diagnosis of WHO grade 4 glioblastoma—which by the way is by definition wild-type for IDH or isocitrate dehydrogenase—~~a~~ny tumors with mutations in the IDH1 or IDH2 gene, even if grade 4 histologically, are no longer considered glioblastoma. Again, GBM or glioblastoma is by definition IDH wild-type now.

So, when we have a new patient who's had either a surgical biopsy or a maximal safe surgical resection of glioblastoma, the standard of care has been largely unchanged since 2005. And that consists of adjuvant radiotherapy with a standard dose being 60 gray delivered in 30 fractions. That's given with concomitant temozolomide chemotherapy, so that's every single day during the six weeks of radiation. And then following a brief four-week treatment break

after radiation and chemotherapy, the standard of care is to resume maintenance cycles of temozolomide, where we do five days on, 23 days off. And we do that for up to six maintenance cycles as the standard.

The only thing that's really changed beyond that core standard of care in recent years is the option to add tumor-treating fields or tumor-treating alternating electrical fields. These are a relatively new treatment modality that was basically established in 2017 in a large phase III trial to improve outcomes when added upon standard of care with radiation and temozolomide. So, alternating electrical fields are sometimes challenging for patients. You need to wear the device on the shaved scalp for a minimum of 18 hours per day on average to deliver the appropriate electrical fields into the tumor to be able to prevent cell division. So, that can be an onerous task on some patients. And therefore, not all patients with glioblastoma choose that part of therapy, but that's essentially been the standard. And with radiation and temozolomide with or without tumor-treating fields, unfortunately, near uniformly, patients will relapse after that treatment and will require salvage therapies in the setting of a recurrent glioblastoma.

Host: While we're talking about challenges, why are brain tumors historically difficult to treat with immunotherapy?

Stephen Bagley, MD: Right. So, with that standard of care I just described, the outcomes are not great. Nobody's being cured and we're not achieving the sort of outcomes that any of us would hope for. And so, as the rest of the world of oncology has really moved into immunotherapy as a standard treatment option across many disease types; in the world of neuro-oncology, this has been incredibly challenging.

I would say one of the only exceptions has been in certain brain metastases, you know, from tumors that classically respond to immune checkpoint inhibitors, like non-small cell lung cancer or melanoma, you sometimes can see responses in the central nervous system metastases to those drugs. But for primary brain tumors, and let's again use glioblastoma as the example, there are myriad challenges associated with immunotherapy.

And if we use the checkpoint inhibitor as the quintessential example, one of the main challenges is that these brain tumors like glioblastoma are immunologically cold at baseline, meaning there is very little in the way of infiltrating T cells. If you look at these tumors in an untreated setting, you know, under the microscope, it's really a T-cell-barren sort of tumor. And there's a number of reasons for that. One is that the tumors tend to have very low tumor

mutational burden or TMB, so there's not a lot of natural neoantigens like there would be in a disease like melanoma.

Other challenges include the blood-brain barrier, of course, getting large monoclonal antibodies like a checkpoint inhibitor across an intact blood-brain barrier is extremely challenging. Another huge problem with glioblastoma in particular is, that the microenvironment is not at all conducive to immunotherapy. There's a large, very large population of cells called tumor-associated macrophages or TAMs. And these TAMs in many patients with GBM can actually account for up to 50% of the entire tumor mass. And so, these cells are highly immunosuppressive and they make life much harder for effector T cells as they're trying to do their job. So, these are just some of the reasons—there are many more—but unfortunately, immunotherapy for glioblastoma really has not panned out despite our field's best efforts thus far.

Host: Well, then tell us about how Penn is leading two studies for gliomas. Break down the first study for us that's using CAR T cells for amplified recurrent glioblastoma.

Stephen Bagley, MD: Sure. So, this is a study that we're all incredibly excited about. And Penn, being one of the first places and a home for CAR T-cell therapy, we've been able to be at the forefront of trying to bring this technology into the world of glioblastoma. We previously conducted two clinical trials of a CAR T cell product that was targeting an antigen on glioblastoma called EGFR variant III or EGFRvIII. And in both of those studies, delivered the CAR T cells through the peripheral blood intravenously. And what we saw in those studies is that the CAR T cells actually did make their way to the tumor. And in many cases, they actually did their job. They were able to target cancer cells that expressed this target antigen, EGFRvIII, and we're able to reduce the population of tumor cells with EGFRvIII.

The problem, and one of the problems at least, is that EGFRvIII is a very heterogeneously expressed target. So, it's only present on a subset of a patient's tumor cells. And in fact, the cells expressing it can change over time. So, you may have a tumor that's floridly positive for EGFRvIII at new diagnosis, and then completely negative once it relapses after radiation and chemotherapy.

So, this problem we call tumor heterogeneity is really one of the main barriers to success that we faced in our first two trials. So, to try to really tackle that issue in particular, my colleagues, Donald O'Rourke and Zev Binder, worked for many years in the lab to develop a bivalent CAR T cell product. So, this is now a product we're putting into patients in the current trial that is

simultaneously targeting two different tumor-associated antigens in glioblastoma. One is EGFR, epidermal growth factor receptor and, in particular, the target is something called EGFR epitope 806, which is basically a conformational form of EGFR that's not normal and is typically only expressed when there is amplification of EGFR or a point mutation in EGFR. You get this unusual confirmation we call epitope 806. And so, one of the antibodies in the CAR construct binds to that particular epitope.

The second is IL-13 receptor alpha-2, which is a well-recognized tumor-associated antigen that we think is expressed in about three-quarters of patients with glioblastoma. So, the idea here is that if we can target both EGFR epitope 806 and IL-13 receptor alpha-2 simultaneously, we have a much higher likelihood of having a meaningful anti-tumor response because we're going after two antigens at once rather than one. And so, that's been the major advance for this trial, with the second advance being that we are now delivering the product intrathecally. So, we implant Ommaya reservoirs in these patients, which are small subcutaneous reservoirs on the scalp that allow us to directly inject the T cells into the patient's spinal fluid. So, we're doing a direct central nervous system delivery, rather than, you know, injecting these through the peripheral blood and sort of hoping that most of them make their way through the blood-brain barrier and into the tumor. So, that's the foundation for the current study, which is actively accruing patients at Penn.

Host: Will you expand a little on what distinguishes this study from previous attempts at CAR T and glioblastoma? Is it just delivery? Is there plenty more? Please expand on that.

Stephen Bagley, MD: So, the delivery part is unique at our institution, given that we had previously done really only peripheral blood delivery, but there are other institutions that are using this intrathecal or intraventricular delivery technique, particularly in pediatric brain tumors across the country.

But what I think is the most exciting part about our study is the bivalent nature of the CAR T cell product and this idea that we're able to tackle two antigens rather than one in the same treatment. This is really the first time in my career that I've seen us actively trying to address this tumor heterogeneity problem, which has really plagued our field as a whole.

Host: Now, talk about the second study, the ATRA, to evaluate the safety and effectiveness of two investigational drugs in treatment-recurrent IDH-mutant glioma. Speak about that a little bit.

Stephen Bagley, MD: Sure. So, this clinical trial is trying to target a completely different population than the one I just discussed. So, the CAR T cell trial is really geared for patients with grade 4 glioblastoma, which as I mentioned, must be IDH wild-type. This second trial involving ATRA—or all-trans retinoic acid—is aiming to treat patients with recurrent IDH-mutant gliomas. And so, gliomas that harbor an IDH mutation are really a completely different disease than glioblastoma. IDH-mutant gliomas tend to happen in younger adults, so they have a different epidemiology. They have a much longer and more indolent natural history, so these tumors tend to be more slow-growing. They can be progressing in a patient for many years before the patient comes to medical attention. And they are initially highly responsive to treatment. So, a patient with a newly diagnosed IDH-mutant astrocytoma or a newly diagnosed IDH-mutant oligodendroglioma, regardless of the grade, whether it's grade 2, 3, or 4, these patients will respond extraordinarily well to radiation and to alkylating chemotherapy such as temozolomide or lomustine.

And they can sometimes go 5, 10, 15 years before having any recurrence or progression of the disease. The problem in these patients is that when they do eventually recur, there is no proven standard of care and we use a variety of different approaches including multiple repeat courses of radiation, we switch to different alkylating chemotherapies. But unfortunately, these tend to be young adults and most of them are going to lose their lives to the disease despite our best efforts. So, there's a huge unmet medical need for better treatments for recurrent IDH-mutant glioma.

So, this clinical trial using all-trans retinoic acid, or ATRA, is developed based on some very interesting science in the laboratory of Nduka Amankulor at Penn, who's been studying and has developed an expertise in IDH-mutant gliomas over many years. And one of the things he really wanted to figure out was, you know, how do these tumors kind of evade the patient's immune system for all of these years as they're slowly progressing in the brain prior to coming to medical attention.

And so, through a variety of elegant experiments, one of the things he figured out was that IDH-mutant tumors are highly deficient in retinoic acid, which is a vitamin A metabolite that is responsible for a variety of normal cellular functions in normal health and also in embryology. But what happens in these IDH-mutant cancer cells is that they're highly deficient in retinoic acid signaling, and because of that, the immune landscape of these tumors is markedly deranged. They're completely barren of T cells. It's almost as if the immune system is ignoring the tumor. And in Dr. Amankulor's animal models of IDH-mutant glioma, when he restores the retinoic acid by administering all-trans retinoic acid or ATRA orally to these mice, what you find in the tumors

when you study them post-ATRA is that you've completely restored normal immune homeostasis. And you end up bringing a lot more T cells in there, and in some of the cases of the mice, actually eradicating their tumors. And so, this was really fascinating work for us to see. And we moved very quickly to translate this into a clinical trial for people with recurrent IDH-mutant glioma. So, we administer ATRA in an oral formulation to these patients, and we're giving it in combination with a PD-1 inhibitor or immune checkpoint inhibitor. With the idea that combining something that is actively bringing T cells into the tumor like ATRA with a PD-1 inhibitor that is further allowing for some of the negative signaling that tends to keep T cells inactive against these tumors, we're restoring that as well. So, we're optimistic that the combination may result in durable immune responses in this patient population.

Host: Absolutely fascinating and very hopeful. Now, what are some of the key findings you're hoping result from these studies? And Dr. Bagley, how do you envision this research translating directly to patient care? Take us from bench to bedside and how this could change the landscape of glioma treatments.

Stephen Bagley, MD: Well, for the CAR T cell trial, this is a first in-human phase I trial. And so, our primary objectives are really to understand the safety, the toxicity profile of this. Is this something that be given to patients with a reasonable side effect profile? And then, we're also trying to figure out what's the right dose. We're studying multiple dose levels here. And what we're learning so far is that when you're delivering it intrathecally, or right into the CNS, you really don't need much. So, the doses of cells we're using here are orders of magnitude lower than what you might use in a patient who's getting treated for leukemia or lymphoma in the blood. And so, we really want to categorize the safety profile and the dose.

But what's been really exciting about this study is that we're already seeing some evidence of tumor shrinkage in some of the patients who've been treated. And so even though it's a phase I, if we're able to detect a promising efficacy signal as well, then that really allows us to push faster in trying to get a phase II trial open and start to move this closer to the point where we can really focus on efficacy, and try to understand how do we optimize this to lead to the best possible patient outcomes. So, I think we're in a very exciting inflection point with regard to that study.

For the IDH-mutant trial of ATRA there, this is a phase II trial, so, you know, because ATRA has been around for a long time and has been used for diseases like acute myeloid leukemia for many years, we really know about the safety profile already. We sort of know what to expect. And so, a true phase I study

wasn't necessary here, and we were able to kind of launch right into a trial that is designed to give us a go/no-go signal or a binary yes/no answer about whether we're actually seeing enough effectiveness here to warrant a larger randomized study in the future. And so, we hope that when this trial is done, we have a positive signal where we're able to say we saw enough here to take this into a randomized setting a multi-center clinical trial.

Host: Thank you so much, Dr. Bagley. As we wrap up here, how can physicians refer a patient that they think would be a good candidate for these trials and what would you like the key takeaways to be?

Stephen Bagley, MD: So, the easiest way to refer patients is to either contact me directly by email at sbagley@pennmedicine.upenn.edu or to contact our nurse navigator, whose name is Molly Cassidy (Molly.Cassidy@pennmedicine.upenn.edu) and her information's available on our Penn Brain Tumor Center website. Either of us, once we receive an initial referral email, we'll get the patient into the queue to be seen typically within one to two weeks and even faster in some cases.

The most important thing for the CAR T cell trial, in terms of eligibility, is that patients need to have an EGFR-amplified tumor. And for the purposes of determining eligibility, we only accept results from one lab, which is a laboratory called NeoGenomics. And so, the earlier that we know about a patient who's a particular possible candidate for this study, we can actually get that process of ordering their tumor tissue testing at NeoGenomics underway as soon as possible. And the faster we get that result back, the faster we can put them in the queue for T cell collection and eventual product manufacturing. So, the rule of thumb with that trial is the earlier we get a referral, the better. And it's smart to even refer patients before they have a recurrence of the glioblastoma. So, for example, if a patient's doing great, has just finished radiation therapy, and there's no signs of the tumor, that's actually the perfect time to send them to us and get them in the queue.

For the IDH-mutant study of ATRA, the same rules apply in terms of getting in touch with myself or our nurse navigator to refer patients. But here, we need to have patients who have a known diagnosis of an IDH-mutant glioma, again, any grade, any histology is okay, and they must have already failed at least radiation. In some cases, they will have also failed chemotherapy, but they need to have at least failed radiation, and then we can evaluate those patients to talk to them about this clinical trial.

Host: Thank you so much, Dr. Bagley, for sharing your incredible expertise with us today. And to refer your patient to Dr. Bagley at Penn Medicine, please call our 24/7 provider-only line at 877-937-PENN, or you can submit your referral via our secure online referral form by visiting our website at pennmedicine.org/referyourpatient. That concludes this episode from the specialists at Penn Medicine. I'm Melanie Cole. Thanks so much for joining us today.