DIPG Update from Dr. Katherine Warren

Clinical Director, Pediatric Neuro-Oncology

Dana-Farber Cancer Institute

November 2019

**Can you provide a brief summary of the latest DIPG research, outcomes and next steps that we can use on the website?**

We are now exploring DIPG as a distinct disease entity. As such, DIPG cell lines and animal models have been and continue to be created, which allow them to evaluate disease biology and response to therapeutics. We now know that DIPG is a heterogeneous disease - not all patients have the same biology, although 80% of children with DIPG have mutations in the histone gene. Most, if not all, also have additional mutations. Recent research is exploring these additional mutations to see how they contribute to tumor formation and growth. Research in DIPG is multi-pronged and is “exploding” compared to historical efforts.

A major area of research is targeting and exploiting the histone\* and chromatin\* abnormalities, and the resulting effects on gene expression and repression. From a clinical perspective, the neuro-oncology community is evaluating whether biopsy is recommended at certain timepoints in the disease course (upfront for enrollment on certain clinical trials, at progression for evaluation of targets, etc.) and if liquid biopsy (sampling blood and/or spinal fluid) can generate sufficient information about the tumor. We are also exploring re-irradiation, molecularly targeted therapies, and different delivery methods such as convection enhanced delivery.

\*Chromatin - the material of which the chromosomes of organisms (other than bacteria) are composed. It consists of protein, RNA, and DNA.

\*Histone - any of a group of basic proteins found in chromatin.

**What is the most promising development that could impact the ability to cure children with DIPG?**

I believe the identification of DIPG as a distinct tumor entity (i.e. different from other pediatric and adult high-grade gliomas) and the subsequent demonstration of the histone mutations/epigenetic abnormalities in most children with DIPG is the most promising development to date. Because of this, we have been able to generate disease-specific cell lines and models to evaluate therapeutics. The current most promising development is high throughput drug screens. Over 4oo active agents have been identified against DIPG. Our task now is to determine an effective dose, how often to give the drug(s), how best to deliver to the tumor site, and how to assess response to the agents.

I also believe immunotherapies will someday play a role in treatment of this disease. This will likely be done as a multifaceted approach, i.e. radiation, molecularly targeted agents and immunotherapies. However, we must first learn how to control the immune response to immunotherapies (i.e. turn it down or off if the response is too vigorous and causes dangerous swelling).

**How have treatment protocols changed in the last 3-5 years?**

While standard of care for children with DIPG continues to be radiation therapy, clinical trials are employed for most patients. Recent clinical trials have been based on molecular targets identified from patient biopsies, as well as agents targeted to the histone mutations.

**What excites you about your role at Dana Farber?**

I am thrilled to be at Dana Farber, an organization that places a priority on children with brain tumors. I have a world-class team whose passion and mission are improving the lives of children with brain tumors and making an impact on the outcomes for these children by increasing survival and quality of life. Additionally, I have access to the brightest minds in medicine and science through collaborations with Boston Children’s Hospital, the Brigham, Mass General, the Broad Institute, MIT, and other institutions. DFCI is supportive of my efforts, including an initiative for establishing the DIPG ALL-In consortium, which will focus on rapidly and rationally translating lab findings to the clinic for children with DIPG.

**What do you hope to achieve realistically in the next 5 years?**

Within the next 5 years, I will establish an expanded pre-clinical evaluation program for DIPG and other pediatric CNS tumors. This will include expanded cell lines and animal models where we can expand our abilities to preclinically assess therapeutics for these children. Using these results, we can more rationally and scientifically design clinical trials and approaches that will give each child a better chance of responding and benefitting from therapy. I plan to establish collaborations within the Harvard and greater Boston scientific communities to expand ideas and out of the box approaches. From a clinical perspective, I plan to develop programs to support the patient beyond tumor therapy as well as their caregivers.

**What research is upcoming?**

As mentioned above, I am establishing the DIPG ALL-In Clinical consortium, which consists of 6 sites within the United States focused on DIPG. We will open our first clinical trial, hopefully by the beginning of 2020. This trial has THE most preclinical data of any prior DIPG study to support its design. The agents have shown preclinical activity alone and together. We have identified an effective dose of each agent, and this will be the starting dose in our trial. This trial will set a precedent in many ways. As it has such extensive preclinical information supporting its use, we will incorporate optional autopsies in cases where it did not appear to be effective in an effort to understand why. However, although this will be a Phase I study to determine safety, tolerability, and feasibility, we hope to see a meaningful improvement in outcome for children with DIPG from this therapy.

**What is the funding outlook like?**

Funding to date primarily relies on foundations and private donors. The DIPG ALL-In initiative has received funding from several sources for its preclinical testing of agents which will be used in this upcoming study and other studies under development. We also have funding from the involved pharmaceutical companies for the first clinical trial. However, funding for the operations of the clinical consortium will need to be raised.

**What can you point to that gives more hope to parents of recently diagnosed DIPG cases?**

A decade ago, children enrolled on clinical trials for DIPG were treated empirically. Today, we now have known targets for DIPG. We have drugs that appear to be active for DIPG. Our goal now is to optimize administration and delivery of these agents to children with DIPG, so we know we are giving adequate doses without causing harm.