Neuro-Oncology
19(9), 1279–1283, 2017



# Letters to the Editor

## Contemporary survival endpoints: an International Diffuse Intrinsic Pontine Glioma Registry study

Our understanding of diffuse intrinsic pontine glioma (DIPG) biology has rapidly evolved in recent years. Promising agents such as panobinostat, with demonstrated disease-specific preclinical efficacy, are currently in clinical trials. Determination of clinical benefit by measuring improved progression-free survival (PFS) and overall survival (OS) requires well-defined historical controls. However, many previous studies evaluating these endpoints included small numbers of patients, were single institution studies, and were not limited to DIPG but rather included all brainstem tumors.[1–4] The most recent study investigating median post-progression survival (PPS) time (ie, time from initial tumor progression to death) in DIPG patients was published over 20 years ago.[5]

We evaluated survival endpoints in patients registered in the International DIPG registry (IDIPGR). Diagnoses of DIPG (defined as tumors with a pontine epicenter and diffuse involvement of at least two thirds of the pons) in patients were made by central radiological review between January 1, 2004 and January 1, 2014. Radiographic progression was determined by central review. PFS was defined as time from date of diagnosis to date of radiographic progression or death from any cause. Time to progression (TTP) was time from date of diagnosis to date of radiographic progression; death was censored. OS was time from date of diagnosis until date of death or censorship. PPS was measured for each patient as OS minus PFS, and for each patient with recorded progression as OS minus TTP. Median and percent survival were estimated using the Kaplan–Meier method.

We identified 372 patients, 235 (63.2%) of whom had documented radiographic progression. Median age at diagnosis was 6.3 years (range 4.6–9.1 y), 55% were female. Caucasian represented the largest portion of racial category (42.7%), followed by other (11.3%), African (9.9%), and Asian (2.4%). Two hundred nineteen patients (58.9%) had symptom duration of less than 6 weeks at diagnosis. Median OS was 11.2 months, consistent with prior reports (Table 1). We found no statistically significant survival differences by age, gender, or racial category.

The IDIPGR, launched in 2012, has enrolled 722 patients to date. By gathering data from larger numbers of patients and including international patient data, outcome studies have larger statistical power and may be more representative of patient outcomes.[6]

Median PPS (OS – TTP) was 4.8 months for the 235 patients with recorded radiographic progression prior to death. For the 137 patients without documented progression, their respective PPS (OS – PFS) measured 0. Median PPS (OS – PFS) as measured for the entire cohort of 372 patients, then, was 2.3 months (Table 1). It is important to understand how differences in survival definition affected results.

This study has several limitations. Although patient enrollment into the IDIPGR requires fulfillment of predefined DIPG diagnostic criteria, clinical-radiographic diagnoses remain vulnerable to subjectivity. A small percentage, 4.6%, of patients had symptom duration of more than 24 weeks prior to diagnosis, begging the question of biologic diversity among registry patients. Clinical and radiographic definitions of progression for patients with DIPG are not standardized and treatment-related changes may complicate interpretation.

This study defines PFS and OS, and is the first to describe post-progression survival in a large cohort of children with DIPG to establish a more reliable historical comparison group for clinical trials. To design trials efficiently and effectively, incorporating the appropriate endpoints is imperative.

**Table 1** Survival endpoints

| | International DIPG Registry Patients | | | | |
|---|---|---|---|---|---|
| | *n* | Median (mo) | 6 Months | 9 Months | 12 Months |
| OS | 372 | 11.2 | 86.6% | 66.1% | 45.3% |
| PFS | 372 | 7.0 | 58.0% | 35.6% | 19.2% |
| OS – PFS | 372 | 2.3 | 25.0% | 13.8% | 7.6% |
| TTP | 235 | 7.0 | 50.2% | 25.8% | 12.4% |
| OS | 235 | 4.8 | 38.2% | 21.0% | 11.6% |

## Funding

We gratefully acknowledge all patients and their families who have supported and contributed to the International DIPG Registry. Supporting foundations include: the Cure Starts Now Foundation, Hope for Caroline Foundation, Julian Boivin Courage for Cures Foundation, Abbie's Army, Michael Mosier Defeat DIPG Foundation, Reflections of Grace Foundation, the Cure Starts Now Australia, Brooke Healey Foundation, Soar With Grace Foundation, Jeffrey Thomas Hayden Foundation, Cure Brain Cancer Foundation, the Jones Family Foundation, Musella Foundation, Pray, Hope Believe Foundation, Smiles for Sophie Foundation, Bennys World, Love Chloe

Foundation, Aidens Avengers, a Cure from Caleb Society, the Operation Grace White Foundation, Ryans Hope, Wayland Villars DIPG Foundation, American Childhood Cancer Organization, Juliana Rose Donnelly Trust, Sheila Jones & Friends, the Ellie Kavalieros DIPG Research Fund, Voices Against Brain Cancer, the DIPG Collaborative. We also acknowledge the support of the Child Health Research Institute, Stanford University.

**Conflict of interest statement.** The authors report no conflict of interest.

**Tabitha Cooney, Adam Lane, Ute Bartels, Eric Bouffet, Stewart Goldman, Sarah E. S. Leary, Nicholas K. Foreman, Roger J. Packer, Alberto Broniscer, Jane E. Minturn, Chie-Schin Shih, Murali Chintagumpala, Tim Hassall, Nicholas G. Gottardo, Hetal Dholaria, Lindsey Hoffman, Brooklyn Chaney, Joshua Baugh, Renee Doughman, James L. Leach, Blaise V. Jones, Maryam Fouladi, Katherine E. Warren, and Michelle Monje**

*Departments of Neurology, Neurosurgery and Pediatrics, Lucile Packard Children's Hospital at Stanford, Stanford, California (T.C., M.M.); Department of Pediatrics, Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (A.L., L.H., B.C., J.B., R.D., J.L.L., B.V.J., M.F.); Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, Canada (U.B., E.B.); Departments of Hematology-Oncology, Neuro-Oncology & Stem Cell Transplantation, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois (S.G.); Department of Hematology/Oncology, Seattle Children's Hospital, Seattle, Washington (S.E.S.L.); Departments of Pediatrics, University of Colorado and Morgan Adams Foundation Pediatric Brain Tumor Research Program, Children's Hospital Colorado, Denver, Colorado (N.K.F.); Center for Neuroscience and Behavioral Medicine, Children's National Medical Center, Washington D.C. (R.J.P.); Department of Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee (A.B.); Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (J.E.M.); Section of Pediatric Hematology/Oncology, Riley Children's Hospital, Indianapolis, Indiana (C.S.S.); Department of Pediatrics, Texas Children's Hospital, Houston, Texas (M.C.); Lady Cilento Children's Hospital, Brisbane, Australia (T.H.); Princess Margaret Hospital for Children and Telethon Kid's Institute, Subiaco, Australia (N.G.G., H.D.); Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland (K.E.W.)*

**Corresponding Author:** Michelle Monje, MD, PhD, 265 Campus Drive G3065, Stanford CA 94305 (mmonje@stanford.edu).

## References

1. Garzón M, García-Fructuoso G, Guillén A, Suñol M, Mora J, Cruz O. Brain stem tumors in children and adolescents: single institutional experience. *Childs Nerv Syst*. 2013;29(8):1321–1331.
2. Salloum R, DeWire M, Lane A, et al. Patterns of progression in pediatric patients with high-grade glioma or diffuse intrinsic pontine glioma treated with bevacizumab-based therapy at diagnosis. *J Neurooncol*. 2015;121(3):591–598.
3. Vallero SG, Bertin D, Basso ME, Pittana LS, Mussano A, Fagioli F. Diffuse intrinsic pontine glioma in children and adolescents: a single-center experience. *Childs Nerv Syst*. 2014;30(6):1061–1066.
4. Wolffe JE, Rytting ME, Vats TS, et al. Treatment of recurrent diffuse intrinsic pontine glioma: the MD Anderson Cancer Center experience. *J Neurooncol*. 2012;106(2):391–397.
5. Packer RJ. Brain stem gliomas: therapeutic options at time of recurrence. *Pediatr Neurosurg*. 1996;24(4):211–216.
6. Baugh J, Bartels U, Leach J, et al. The International Diffuse Intrinsic Pontine Glioma Registry: an infrastructure to accelerate collaborative research for an orphan disease. *J Neurooncol*. 2017;132(2):323–331.


doi:10.1093/neuonc/nox107

# Absence of CMV viremia in high-grade glioma patients under low dosage glucocorticoid treatment

Cytomegalovirus (CMV), a life-threatening infectious pathogen in immunosuppressed patients, is a hot topic in the evolution and treatment of high-grade gliomas. Goerig et al[1] showed recently that the reactivation of CMV is common and associated with radiotherapy (RT) and the dosage of dexamethasone intake administered before or during RT. In this study we attempted to validate this finding by screening high-grade glioma patients ($n$ = 29) for presence of CMV viremia and anti-CMV immunoglobulins in relation to selected clinical information.

The present cohort of patients with glioblastoma included patients with World Health Organization (WHO) grade IV ($n$ = 27), anaplastic astrocytoma grade III ($n$ = 1), and anaplastic oligodendroglioma grade III ($n$ = 1) who were studied in the Vienna Cancer and Thrombosis Study (CATS).[2] Patients enrolled in this analysis were diagnosed and treated in the years 2011–2013 at the Medical University of Vienna. Serum samples of these patients were taken for 6 months every 4 weeks, starting during RT and treatment time and stored at –80°C. Clinical information was assessed