Characteristics of Patients ≥ 10 Years of Age with Diffuse Intrinsic Pontine Glioma: A Report from the International DIPG Registry

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Background

Median age of patients with a diffuse intrinsic pontine glioma (DIPG) is 6-7 years old, and the median survival is less than 1 year.

Patients ≥ 10 years of age with a DIPG are reported to have a higher rate of long-term survival (≥24 months) and reasons for the longer survival are unclear.

The purpose of this study was to:
A) Define DIPGs in patients ≥ 10 years of age with regards to clinical, radiological, pathological and molecular characteristics.
B) Compare patients ≥ 10 years of age who are long-term survivors (LTS) with those that are short-term survivors (STS) using clinical, radiological, pathological and molecular characteristics.

Methods

Data were abstracted from the International DIPG Registry for patients ≥ 10 years of age for all available data of clinical, radiological, pathological and molecular characteristics.

The primary outcome was overall survival (OS) categorized as LTS (≥24 months) or STS (<24 months).

Patients ≥ 10 years of age were excluded from the analysis if:
- Excluded by central imaging review
- No imaging available for central review
- Did not receive upfront radiation therapy
- If patient alive but not ≥24 months
- Did not receive upfront radiation therapy
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Patient characteristics are summarized using median and ranges or frequencies and percentages. Univariable analyses were performed using Fisher’s exact test, Chi-squared test or Wilcoxon rank sum test. Survival was estimated using the Kaplan-Meier method, and the survival of patients ≥ 10 years of age was compared to the historical survival median using a one sample proportion test. Statistical evaluation was performed using R (version 3.1.3). P < 0.05 was considered significant.

Discussion

- About 21% of patients diagnosed with a DIPG are ≥ 10 years of age.
- Patients ≥ 10 years of age with DIPG differ from historical controls:
  a) more likely to have a longer duration of symptoms prior to presentation
  b) less likely to have cranial nerve palsies or pyramidal tract signs at diagnosis
  c) less likely to have nécrosis at diagnosis
  d) more likely to have improved overall survival
- In patients ≥ 10 years of age with DIPG about 1/3 of patient had tissue either via biopsy or autopsy.
- For patients ≥ 10 years of age with DIPG, LTS were more than 50% more likely to have longer symptom duration and larger tumors at presentation.
- The presence or absence of histone mutations did not differ between LTS and STS cohorts, but sample size is small.
- Central imaging review is helpful to determine atypical features and guide cases where biopsy may be helpful to include or exclude diagnosis.
- This is the largest cohort of patients analyzed of DIPG patients who are ≥ 10 years of age and provides important information about this patient population.
- Further acquisition of genomic and bio data may help us better understand this older group of patients with DIPG.

References

Clinical, radiological, pathological and molecular characteristics of children ≤3 years with diffuse intrinsic pontine glioma (DIPG): a report from the International DIPG Registry (IDIPGR)

Allison Barrett, Adam Lane, Nancy Yanez-Escorza, Brooklyn Cheney, Anne Cochrane, Craig Erker, Renee Doughman, Marko Doce-Ruiz-Schmutzler, Stuart Goldman, Kathy Warren, Pratiti Bandopadhayay, Chie-Schin-Shih, Jane Minturn, Ute Baraib, Cynthia Hawkins, Roger Packer, Javad Nazarian, Tim Hassall, Yvan Samson, Michelle Monge Daou, South, Paul Fisher, Lars Wagner, Craig Koschmann, David Ziegler, Mark Kieran, Cynthia Hawkins, Peter White, Phillip Doshimer, Jacob Hendershot, Rachid Drissi, Christine Fuller, James Leach, Blaise Jones, Maryam Fouladi

BACKGROUND

- The prognosis for children diagnosed with Diffuse Intrinsic Pontine Glioma (DIPG) remains grave, with median survival less than 1 year
- Children diagnosed with DIPG ≤3 years of age are reported to have a higher rate of long-term survival (LTS, overall survival (OS) >24 months)
- The factors contributing to the observed improvement in this age group remain unknown
- The purpose of our study was to examine patients ≤3 years of age with centrally confirmed DIPG, to compare clinical, radiological, histological and molecular characteristics between LTS versus short-term survivors (STS <24 months)

METHODS

- Patients ≤3 years of age were abstracted from the International DIPG Registry (IDIPGR)
- For each patient, all available information surrounding their clinical course, radiological features, pathological and molecular characteristics was obtained
- The primary outcome was OS, with LTS defined as ≥24 months, and STS <24 months
- Patients who met the age criteria were excluded from our analysis if:
  - No imaging was available for central review
  - Imaging was not consistent with DIPG on central radiology review
  - Biopsy histology was inconsistent with DIPG
  - Clinical data was unavailable
  - Patient is living, but less than 24 months has passed since their diagnosis
  - Date of death is unknown
- Univariate analyses were performed using Fisher’s exact test or Wilcoxon rank sum test
- Survival was estimated using the Kaplan-Meier method
- Statistical evaluation was performed using R (version 3.1.3), \( P < 0.05 \) was considered significant

RESULTS

- Children ≤3 years of age with DIPG maintain a higher rate of LTS
- They are a distinct population, with an improved median survival of 16 months and a higher rate of LTS
- 29% of children diagnosed with DIPG at ≤3 years of age are LTS
- Children ≤3 years of age with DIPG maintain this improved survival at 3, 4 and 5 years from diagnosis
- Compared to significant predictors of LTS in historical controls, children with DIPG at ≤3:
  - similarly show short symptom duration (<6 weeks) in STS
  - decreased frequency of cranial nerve palsies at diagnosis
  - increased frequency of necrosis on diagnostic imaging
  - lower frequency of H3K27M mutants
- We did not observe any significant radiographic predictors of LTS or STS
- Biologic analysis has not yet revealed predictive markers
- Analysis of patients who did not receive any therapy revealed a decreased median survival of 2 months, and 1 LTS
- Patients excluded on central review had decreased median survival of 10 months
- Ongoing genomic analysis and data acquisition will be important in gaining greater understanding of this unique patient population

DISCUSSION

- Children ≤3 years of age represent 7% of all patients diagnosed with DIPG
- They are a distinct population, with an improved median survival of 16 months and a higher rate of LTS
- 29% of children diagnosed with DIPG at ≤3 years of age are LTS
- Children ≤3 years of age with DIPG maintain this improved survival at 3, 4 and 5 years from diagnosis
- Compared to significant predictors of LTS in historical controls, children with DIPG at ≤3:
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- Biologic analysis has not yet revealed predictive markers of LTS, though small sample size
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- Ongoing genomic analysis and data acquisition will be important in gaining greater understanding of this unique patient population

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REFERENCES

Medulloblastoma therapy generates risk of a poorly-prognostic H3 wild-type subgroup of diffuse intrinsic pontine glioma: A report from the International DIPG Registry

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BACKGROUND:
Medulloblastoma and diffuse intrinsic pontine glioma (DIPG)

• With improved survivorship in medulloblastoma, there has been an increasing incidence of late complications, including those related to treatment, which includes high doses of external beam radiation therapy.
• No previous studies have assessed the risk of the development of radiation-associated DIPG in medulloblastoma survivors, which could impact the future dose and modality of radiation therapy in future clinical trials.
• Approximately 80% of radiation-naïve DIPGs harbor a point mutation in the histone H3 (H3.3 and H3.1), which is associated with epigenetic dysregulation of neurodevelopmental pathways and a worse prognosis than H3 wild-type DIPG.
• There is a paucity of data specifically addressing the molecular characteristics of radiation-associated DIPG among medulloblastoma survivors.

OBJECTIVE:
To estimate the risk and characterize the molecular features of radiation-associated DIPG among pediatric medulloblastoma survivors.

Histology and molecular results distinguish primary medulloblastoma from radiation-associated DIPG

CONCLUSIONS
• DIPG is not an infrequent complication of medulloblastoma therapy (cumulative incidence of 0.3% to 3.9%).
• Sequencing studies of cases with available tissue revealed a distinct molecular subgroup of H3 wild-type DIPG with recurrent mutations that largely did not overlap with known pediatric glioma drivers but highly overlapped with mutated drivers of adult GBM.
• In spite of H3 wild-type status, a strong positive prognostic factor in DIPGs, patients with radiation-associated DIPG had a significantly worse median overall survival compared to patients with primary DIPG.