What's New in Pediatric Brain Tumors

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Brain Tumor Statistics

- Central Brain Tumor Registry of the United States reports the annual incidence of primary brain tumors in children ages 0-19 years is 6.14 per 100,000. (1)
- Pediatric brain tumors are the second most common malignancy of childhood after acute leukemia.(1)
- Pediatric brain tumors continue to be the number one cause of cancer-related mortality in children in all age groups.
- Pediatric Oncology rely heavily on consortiums, like Children's Oncology Group (COG) to aid advancing treatment in these rare tumors.
- Per COG reports, less than 5% of adults with cancer enroll in clinical trials and over 60% of patients under the age of 29 years enroll in clinical trials.

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Brain Tumor Specific Consortiums

- Pediatric Brain Tumor Consortium (PBTC) was founded in 1999 and includes over 14 pediatric hospitals. Their focus is Phase 1 and Phase II trials with phase III being coordinated with COG. (2)
- Pacific Pediatric Neuro-Oncology Consortium (PNOC) is an international pediatric brain tumor consortium that focus on early phase clinical trials.
- Pediatric Oncology Experimental Therapeutics Investigators Consortium (POETIC) includes 10 institutions across the US and Canada and its focus is early clinical trials and genomics translation programs.
- The Children's Brain Tumor Network (CBTN) brain tumor tissue bank and database that includes clinical, genomic, and histology data.

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Molecular Diagnostics

- Advanced molecular diagnostics, such as methylation profiles, whole genome sequencing, and transcriptomics, has led to the discovery of molecularly-defined tumor types over the past decade.
- Methylation profiling provides insight into why the gene may be expressed at a given level.
- Whole genome sequencing looks at entire genome.
- Genotyping studies change within the sequence.
- Transcriptomics studies the organism transcriptome (all RNA molecules in a cell).
- Histones are proteins that form complexes known as nucleosomes that wrap and condense DNA into chromatin. (3)

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Molecular characterization of common brain tumors in pediatrics

Medulloblastoma

Most common malignant brain tumor in children, accounts for ~40% of all posterior fossa tumors of childhood (4)

4 molecular subgroups: WNT, SHH, Group 3, Group 4 (5)

Classifications

WNT: activated WNT pathway signaling this sub-group makes up 10% of Medulloblastomas and has a very good prognosis of > 90% 5year overall survival. (6)

SHH: named after the affected pathway. 10-15 % of Medulloblastomas. Intermediate prognosis 5year overall survival is 77% in infants and 68 % in children

Group 3: make up 25 % of medulloblastoma tumors. Most often metastatic at diagnosis. It is most aggressive and prognosis less than 60% overall 5year survival.

Group 4: Most common and make up 35-50%. Least well understood. Intermediate prognosis. 75% overall 5year survival.

Medulloblastoma therapy includes surgery, radiation and chemotherapy *(6)*

<u>COG Chemotherapy Trials:</u>

ACNS0331: focused on limited target volume boost radiation with reduced cranial spinal radiation in standard risk medulloblastoma with a goal to reduce neurocognitive effects.

ACNS0332: focused on whether a radio sensitization with carboplatin in addition to vincristine improves cure rates for high risk medulloblastoma.

ACNS0334: Children < 36 months with HR medulloblastoma were studied with the addition of HD MTX to intensify induction followed by consolidation cycles with stem cell rescue**.**

Most recent trials focus on de-escalating therapy on average risk WNT subgroups

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Ependymoma

Accounts for 10% of all childhood CNS tumors with incidence of 2.2 cases per million. 5year survival of 84% and 10year survival of 79%. (7)

2016 WHO classification of CNS tumors includes Ependymoma, RELA fusion positive as the only genetically defines sub type. However, there are several groups that have gone further to establish 9 distinct sub-groups.

Subtypes: Myxopapillary, subependymoma, papillary, classic, and anaplastic.

Treatment

Treatment of ependymoma relies on maximal surgical resection followed by radiation. The use of chemotherapy has been controversial.

ACNS0831: this protocol was to evaluate whether or not the addition of maintenance chemotherapy followed by radiation would improve survival, final analysis is ongoing.

Diffuse Intrinsic Pontine Glioma (DIPG)

200-400 children diagnosed in the US every year

Accounts for 10 % of all brain tumors in children (Ages 4-11y)

Treatment: Radiation (no chemotherapy options have increased overall survival)

Progression free survival 6-9 months with <1% 5year survival

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2011-2015 a study was completed to assess the safety of surgical biopsy of the pons. 50 pts across 23 institutions revealed 1 patient had long term neurological deficits.

Whole genome sequencing and methylation profiling found that 80% of DIPG's have a mutation (K27M-H3.3 or K27M-H3.1).

Panobinostat was a promising agent for DIPG with the possible mechanism of restoring H3K27M and normalizing oncogenic gene expression. (9)

PNOC is conducting a phase I/II trial with a formulation of Panobinostat being injected via a catheter directly into the tumors.

PNOC is also conducting a multi-center, target validation study of fimepinostat.

There is also a phase I trial of Panobinostat in conjunction with Marizomib.

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Atypical Teratoid Rhabdoid Tumor (ATRT)

Highly aggressive tumors typically seen in children <3 years of age and is the most common malignant tumor in children <6months old.

Overall survival has improved with multimodal therapy and is now 55-60% 5year survival.

Molecular characterization has led to many clinical trials using inhibitors. A phase 1 study using an inhibitor (Tazemetostat) has had an overall good response rate of 17%.

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Low Grade Gliomas (LGG)

Pediatric LGG differ from adults as far as treatment, prognosis and molecular characterization.

60% of patients that undergo a gross total resection will never have a recurrence. Of those that have residual tumor or recurrent tumors have a 46%-89% 5year overall survival.

Radiation stabilizes approximately 70% of tumors (however this is not used as standard of care due to co-morbidities and long-term neurocognitive effects.

Low grade gliomas are characterized by alterations in the BRAF gene which leads to an activation of the MAPK pathway (not seen in adults).

BRAFV600 is seen in 17%-50% of pediatric low-grade gliomas and is thought to have a poorer prognosis.

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Targeted therapies have made a significant impact on the treatment of pediatric low-grade gliomas and have the potential to surpass current standard of care chemotherapy.

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Immunotherapy

Recent studies have evaluated the use of immunotherapy. Results have not been promising as they are in adult medicine or pediatric leukemia.
Multiple approach vaccine trials are ongoing for pediatrics. PNOC is conducting a phase study with H3.3K27M peptide vaccine with nivolumab for DIPG patients.

CAR T cell Trials are on going. There are many open trials currently such as A HER2-CAR for HER2 + CNS tumors (recurrent or refractory) and it is injected directly into the ventricles or resection cavity.

Checkpoint blockade treatment is also in active research. Checkpoint molecules are proteins found on the surface of T cells that help in the regulation of immune response.

There is a phase 1 trial being conducted by PBTC on an anti-PD1 for recurrent for recurrent or progressive DIPG's, high grade gliomas, ependymomas, and medulloblastomas.

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Long Term Outcomes

Overall, pediatric brain tumor outcomes have improved. With the improved outcomes there has been a focus on the long-term outcomes.

There have been many studies looking into the long term effects of radiation therapy.

St. Jude reviewed over 194 children's records who were diagnosed 1985-1999 who received CSI. 71% of children who received CSI had severe intellectual disability.

There is a focus in several clinical trials to reduce or eliminate radiation therapy because of the long term effects on children.

HeadStart trials focus on intensifying chemotherapy followed by stem cell rescue in order to avoid radiation therapy.

Proton radiotherapy is recommended with radiation therapy cannot be avoided.

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Pediatric brain tumors are the second most common cancer in children and unfortunately the leading cause of cancer related deaths.

Progress continues to be made by understanding the biology of these tumors, the high percentage of clinic trial enrollment, and the multiple consortiums and foundations that support pediatric brain tumors.

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