Medulloblastoma – A new era of diagnosis

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Disclosures

- None
Learning Objectives

1. Medulloblastoma background and current standard of care
2. Effects of brain irradiation in infants and young children
3. Medulloblastoma as a heterogenous disease – Molecular subtypes
4. Conclusion
Brain Tumors in Children

• The second most common type of cancer in children

• Leading cause of cancer morbidity/mortality in childhood\(^1\)

• After accidents, homicides and suicides, the most common cause of death in children between 1 and 16 years of age in North America and Western Europe

Medulloblastoma

- Highly malignant, invasive embryonal tumor of the cerebellum\(^1\)
  - Predominantly neuronal differentiation
  - Inherent tendency to metastasize via CSF pathways
  - Heterogenous

Epidemiology - Medulloblastoma

- Most common malignant brain tumor in children (20%)
- Peak incidence between 5 - 7 years of age
- <1% of brain tumors in adults
Diagnosis - MRI

• On MRI
  – Hypointense on T1WI
  – Hypointense on T2WI
  – Heterogeneously contrast enhancing
  – Drop mets are usually contrast enhancing and have a “sugar coated” appearance

Diagnosis - Pathology

• Medulloblastoma – WHO Grade IV tumor
  – Classical MB
  – Desmoplastic/nodular MB
  – Medulloblastoma with extensive nodularity (MBEN)
  – Anaplastic MB
  – Large Cell MB

• Outcome highly associated with histology
Medulloblastoma – Risk Stratification

• Dissemination
• Age -> 3 years and < 3 years old
• Extent of resection – GTR: <1.5 cm$^2$ (COG) or R0: no residual tumor (HIT, Head Start)
Medulloblastoma
Risk Stratification

• Dissemination:
  – CSF
  – MRI of the brain and spine

• Modified Chang M-staging system for disseminated disease:
  – M0: No evidence of dissemination
  – M1: Disseminated tumor cells in the CSF
  – M2: Radiologic (MRI) cranial metastasis
  – M3: Radiologic (MRI) spinal metastasis
  – M4: Extra-neural spread
Medulloblastoma - Risk Stratification

Standard Risk Medulloblastoma
• No evidence of neuraxis dissemination
• No evidence of extraneural dissemination
• Gross total surgical resection of primary site tumor, confirmed on post-op brain MRI

High-Risk Medulloblastoma
• Any or >1.5 cm² residual tumor diameter post-operatively
• Evidence of neuraxis dissemination
• Evidence of extraneural dissemination
Treatment for HR MB and PNET in Patients >3 years of age

- **3600 cGy CSI** + PF boost to 5400 cGy along with weekly vincristine *followed by* CCNU or cyclophosphamide, cisplatin, and vincristine (Packer regimen)

- **3600 cGy CSI** + PF boost followed by 4 cycles of high dose chemotherapy: cyclophosphamide, vincristine, cisplatin with autologous hematopoietic stem cell rescue (SJMB96)

- **3600 cGy CSI** + PF boost with weekly vincristine and daily carboplatin followed by 6 cycles of chemotherapy with cyclophosphamide, cisplatin, and vincristine (CCG 99701)
## Survival on High Risk medulloblastoma Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>5-Year PFS (%) ± SD</th>
<th>5-Year OS (%) ± SD</th>
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<tbody>
<tr>
<td>Full dose CSI + Packer Regimen¹</td>
<td>67 ± 15 (M+)</td>
<td>83 ± 6</td>
</tr>
<tr>
<td>(CCNU, cisplatin, vincristine)</td>
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<tr>
<td>SJMB96²</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>CCG 99701 [Abstract 2007 - preliminary data]³</td>
<td>66 ± 6 (4 years)</td>
<td>81 ± 5 (4 years)</td>
</tr>
</tbody>
</table>

Treatment for SR MB in Patients >3 years of age

- **2340 cGy CSI** + entire posterior fossa boost to 5400 cGy along with weekly vincristine followed by maintenance chemotherapy using CCNU or cyclophosphamide, cisplatin, and vincristine (COG A9961)

- Two courses of eight drugs in 1 day followed by 2 courses of carboplatin and VP-16 followed by **2500 cGy CSI** and boost (SFOP)

- **2340 cGy CSI** + boost followed by 4 cycles of high dose chemotherapy with autologous hematopoietic stem cell rescue (SJMB96)

## Survival on Standard Risk medulloblastoma Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>5-Year PFS (%) ± SD</th>
<th>5-Year OS (%) ± SD</th>
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<tbody>
<tr>
<td>COG A9961¹</td>
<td>81 ± 2.1</td>
<td>86 ± 9</td>
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<tr>
<td>SFOP²</td>
<td>64.8 ± 8.1</td>
<td>73.8 ± 7.6</td>
</tr>
<tr>
<td>SJMB96³</td>
<td>83</td>
<td>85</td>
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Medulloblastoma Outcomes Improving

<table>
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<tr>
<th>5 year PFS</th>
<th>1980</th>
<th>2010</th>
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<tr>
<td>Standard Risk</td>
<td>55%</td>
<td>85%</td>
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<tr>
<td>High-Risk</td>
<td>35%</td>
<td>70-80%</td>
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At What Sacrifice???
The Effects of Radiation Therapy on the Developing Brain of the Young Child

- Learning difficulties.
- Attention/concentration difficulties.
- Short-term memory deficits.
- Social adjustment problems.
- Hearing, speech and language problems.
- Impaired physical growth (hypothalamus, pituitary, spine).
- Secondary malignancies
Irradiation: Cognitive Deficits

• 1964-1976: 44 children with medulloblastomas treated with radiotherapy to entire CNS

• The 5-year OS was 54% in the whole series

• Life of survivors: impaired by mental or behavioral disturbances.
  
  – Large decreases in IQ
    • 70 to 90 in 58%
    • < 70 in 31%

Hopital des Enfants Malades of Paris Experience

• 59 children (14% under the age of 3 yrs) treated between 1975-1990
• All patients received 3600 cGy CSI + Post Fossa Boost
• 85% of patients IQ < 90 at 10 years post treatment

The Ongoing Effects of Irradiation

• Neurocognitive decline
• Hormonal deficiencies
• Growth decline
• Secondary malignancies
Radiation Therapy: Devastating in children < 4yrs

• A retrospective, multi-center Canadian study:
  – all surviving children with brain tumors who received cranial xrt at < 4 years of age:
    • 222 patients (1958-1995)
    • Investigated focal neurological deficits, hearing, vision, education, occupation, living arrangements
  – Only 1/3 adult survivors were able to have a “normal life style”

• Sequelae of craniospinal irradiation are unacceptable in the youngest children!

Chemotherapy Only Strategies for Young Children with Newly-Diagnosed Malignant Brain Tumors
Treatment of Children < 3yrs with Medulloblastoma

- Event-free survival is poor with conventional chemotherapy strategies attempting to either delay (Baby POG 1\(^1\)) or avoid irradiation (CCG-921\(^2\); CCG-9921\(^3\); BB-SFOP\(^4,5\)):

- Medulloblastoma = \(<10-33\%\) 2 to 5 year EFS

Treatment for MB/CNS-PNET in Patients <3 years of age

• Conventional chemotherapy with systemic and intraventricular methotrexate without irradiation – HIT’ 92

• Intensive induction chemotherapy (+/- high-dose methotrexate) followed by myeloablative chemotherapy – “Head Start”

• Conventional chemotherapy followed by 3 tandem autologous hematopoietic stem cell transplants – CCG99703


Multi-institutional/multi-national prospective clinical trials, currently involving 39 participating institutions throughout U.S.A., Canada, Australia, New Zealand and Argentina.
Head Start Treatment

- Radical tumor resection at diagnosis (if feasible)
- Five cycles of Induction chemotherapy
- Harvest & cryopreserve peripheral blood stem cells (PBSCs) after 1st cycle
- Resection of residual tumor after 4 to 5 cycles
- Single Consolidation cycle of high dose chemotherapy (HDCx: thiotepa, etoposide & carboplatin) followed by autologous stem cell rescue (ASCR)
Head Start Strategy

• **Avoidance** of brain irradiation in children achieving complete responses to initial treatment and less than 6 years of age

• **Reduction** in the doses and volume of brain irradiation for those children with incomplete responses to initial treatment, or those over 6 years of age at diagnosis
Treatment Schema: Head Start I/II

**Head Start I:**
- Cisplatin
- Cyclophosphamide
- Vincristine
- Etoposide IV

**Head Start II**
- HS I Induction + HD Methotrexate IV
- For metastatic disease only
- X 5 Cycles

**Second Look Surgery**
- HD chemo /AHCRx1

**Induction**
- Thiotepa 300 mg/M²/day X 3 days
- Etoposide 250 mg/M²/day X 3 days
- Carboplatin AUC =7/day X 3 days

**Surgery**

**Second Look Surgery**

**+- Irradiation**
EFS and OS for HS I/II

Medulloblastoma
Head Start II: Comparison of Neuropsychological Functioning Over Time

• A comparison of mean IQ between baseline and time 2 assessment for 12 patients
Future Staging for Optimal Treatment

• Can certain subgroups of patients receive less radiation therapy?
• Less chemotherapy?
• Biological targeted therapy?
Histology as a Staging Tool – Desmoplastic Medulloblastoma

- 260 patients (Germany, France, Italy, USA, UK) < 5 yrs
- Desmoplastic Medulloblastoma associated with better outcome in young children

Histology as a Staging Tool- Anaplastic Medulloblastoma

- EFS for A9961 per anaplasia
- Overall Survival was statistically significant: 89% versus 75%. $P = 0.005$

- EFS for SJMB96 per anaplasia
- 5 yr EFS was statistically significant: 84% versus 57%. $P = 0.04$
Clinical risk based on histology

• Does not reflect the differences that exist within the same histological variants of medulloblastoma
## Important signaling pathways in medulloblatoma

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<tr>
<td></td>
<td></td>
<td>– Sonic Hedgehog (SHH)</td>
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<tr>
<td></td>
<td></td>
<td>– Wingless Pathways (Wnt)</td>
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Current Molecular Classification

• Understanding of medulloblastoma biology has improved by high-throughput genomic and proteomic methods
  – Genomic studies over the last 9 years have demonstrated that medulloblastoma consists of biologically distinct subgroups of tumors.
• Consensus: 4 clinical and molecular subtypes of disease.
Subgroups of Medulloblastoma

- Wnt subtype
- Sonic Hedgehog subtype (SHH)
- Group 3
- Group 4
  - Demographic, transcriptional, genetic and clinical differences among these 4 disease subtypes
  - Wnt subtype: 5 yr OS > 90% with current standard therapy
  - Group 3 subtype: 5 yr OS 40-60%
Molecular Subgroups
Wnt Subtype

- Rarest subgroup – 10% of medulloblastomas
- All have nuclear accumulation of β-catenin – Leads to activation of canonical Wnt-signalling pathway.
- Genomic Features: monosomy of chromosome 6
  - Driver genes: CTNNB1 (90.6%), DDX3X (50%), SMARCA4 (26.3%)
- Clinical Features
  - Most common in older children and adolescents. Rare in infants
  - Histology: classic, very rarely anaplastic
  - 5 yr OS ~ 95%
- Treatment: Future studies to determine if we can decrease radiation and/or chemotherapy in these patients

Gajjar et. al., Nature Reviews Clinical Oncology, 2014
SHH Subtype

- 30% of medulloblastomas
- Tumors characterized by activation of SHH signaling are associated with variety of genetic aberrations, histological features and clinical presentations
- Heterogeneity depends on age of diagnosis and genetic alterations
- All have increased SHH signaling
- Chromosomal gains and losses: frequent loss of 9q, 10q and 17p; gain of 3q and 9p
- Driver genes: PTCH1 (28%) TP53 (13.6%) KMT2D (12.9%) DDX3X (11.7%) MYCN amplification (8.2%)
• Clinical features:
  – Incidence: Bimodal – first peak in infants and young children (< 5 years), second peak in older adolescents and adults (> 16 years); less common in children in 5-16 yrs
  – Histology: represented by all histological phenotypes
  – 5 yr OS ~ 75%
  – Treatment based on age and mutations
    • Infants have great OS
    • Tumors with MYCN and GLI2 amplifications have dismal prognosis

Gajjar et. al., Nature Reviews Clinical Oncology, 2014
Group 3 Subtype

- 25% of medulloblastoma
- Worst outcome amongst all the subgroups
- Incidence: occurs predominantly in infants and young children
- Histology: classic > large/anaplastic
- Expression signature: MYC
- Chromosomal gains and losses: frequent loss of 10q, 16q and 17p, gain of 1q, 7, 17q, 18
- Driver genes MYC amplification, PVT1 amplification, SMARCA4, OTX2, CTDNEP1, LRP1B
- 5 year OS ~ 50%

Gajjar et. al., Nature Reviews Clinical Oncology, 2014
Group 4 Subtype

• 35% of medulloblastomas
• Seen in all age groups
• Underlying biology not well understood
• Incidence: children (median age ~ 9 years)
• Histology: classic; large cell/anaplastic
• Chromosomal gains and losses: loss of 8, 10, 11 and 17p; gain of 4, 7, 17q and 18
• Driver genes: KDM6A; SNCAIP gain; MYCN amplification; KMT2C; CDK6 amplification; ZMYM3
• 5 yr OS ~ 75%

Gajjar et. al., Nature Reviews Clinical Oncology, 2014
Future Treatment Directions

- Molecular subtype based therapies
- Possible reduce radiation therapy and chemotherapy for some groups
- Add novel targeted therapies for others
Final Conclusions

• Medulloblastoma are the most common malignant tumors of childhood

• Overall survival has improved with the use of radiation therapy and chemotherapy
  – Unfortunately, at the expense of severe neuro-cognitive late effects

• Myeloablative chemotherapy with autologous stem cell rescue is a feasible and successful alternative for infants and young children with brain tumors

• The future direction of medulloblastoma treatment is to stratify treatment based on the new molecular classification of this heterogenous disease.