Systemic Therapy for Medulloblastoma

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Outline

- Evolution of Chemotherapy in Medulloblastoma
- Principles of chemotherapy
- Optimization of chemotherapy
- Risk Stratification
- Chemotherapy in Average Risk
- Chemotherapy in High risk group
- Chemotherapy in Infants & young children
- Recurrent medulloblastoma
- Future of Systemic therapy
Team Work

100%

Targeted Therapy

Conventional CT
70-80%

RT
50-60% survival

Surgery
10-20% survival
Evolution of chemotherapy

- Pre-1930 era: Surgery alone was used with less than 10% survival and median survival of 12 months

- Bailey and Cushing: pioneered used of whole neuraxis irradiation in 1930 with dramatic improvement in survival to 50-60% by 1980s

- Van EysJ introduced chemotherapy with negative results (Can treat reports, 1981)

- First randomized studies in 1990 by SIOP & CCG established role of chemotherapy in high risk population

- Packer et al in 1999 proved the role of chemotherapy in average risk Medulloblastoma in decreasing the CSI dose with out detriment in survival
Principles of Chemotherapy

- Chemotherapeutic agents should be lipid soluble, less protein bound and less ionized
- Co-administration of agents decreasing activity through CYPP3A4 induction such as Phenytoin, phenobarbitone and steroids are avoided
- Concomitant RT may be useful by increasing the transcapillary transport
Optimising Systemic Therapy

• Established:
  – high dose chemotherapy
  – Intrathecal therapy
  – Radiosensitization

• Experimental:
  – Intratumoral therapy
  – Intraarterial therapy

• Novel approaches:
  – Differentiating agents
  – Gene therapy
  – Antiangiogenesis
  – Targeted agents
## Risk-Adapted Approach

<table>
<thead>
<tr>
<th>Factor</th>
<th>Standard-risk</th>
<th>High-Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>&gt;3yr</td>
<td>&lt;3 Yr</td>
</tr>
<tr>
<td>Extent Surgical resection</td>
<td>&lt;1.5cm²</td>
<td>&gt;1.5cm²</td>
</tr>
<tr>
<td>stage</td>
<td>M0</td>
<td>≥M1</td>
</tr>
</tbody>
</table>

Europe: Age and M stage (M1 vs ≥ M2)
Standard-Risk: Traditional Standard

- Maximum surgical resection (GTR) → craniospinal RT (CSI) ± chemotherapy
- RT dose CSI 36Gy, PF dose 55.8Gy
- Chemotherapy is commonly practiced outside a trial
- Preradiation (Neoadjuvant RT/Sandwich) CT in Europe vs Adjuvant in USA
- 75-80% EFS
- High incidence of late neuroendocrine and neuropsychiatric morbidity
# Standard-Risk: Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Accrual period</th>
<th>Eligible patients</th>
<th>Treatment (Gy, posterior fossa/craniospinal axis)</th>
<th>Progression-free survival at 5 years (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIT ’91</td>
<td>1991–97</td>
<td>118</td>
<td>ifosfamide, etoposide, methotrexate, cisplatin, cytarabine preradiation (55·2/35·2) vs vincristine, lomustine, cisplatin postradiation (55·2/35·2)</td>
<td>65 vs 78</td>
<td>&lt;0·03</td>
</tr>
<tr>
<td>SIOP III</td>
<td>1992–2000</td>
<td>179</td>
<td>Radiation (55/35) vs vincristine, etoposide, carboplatin, cyclophosphamide preradiation (55/35)</td>
<td>60 vs 74</td>
<td>0·036</td>
</tr>
<tr>
<td>CCG9892</td>
<td>1990–94</td>
<td>65</td>
<td>Vincristine, lomustine, cisplatin postradiation (55·2/23·4)</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>SJMB’96</td>
<td>1996–99</td>
<td>34</td>
<td>High-dose cyclophosphamide, cisplatin, vincristine postradiation (55/23·4)</td>
<td>94†</td>
<td></td>
</tr>
<tr>
<td>POG8631/CCG923</td>
<td>1986–90‡</td>
<td>81</td>
<td>Radiation (54/36) vs radiation (54/23·4)</td>
<td>67 vs 52</td>
<td>0·14$</td>
</tr>
</tbody>
</table>
Phase III Study of Craniospinal Radiation Therapy Followed by Adjuvant Chemotherapy for Newly Diagnosed Average-Risk Medulloblastoma


Purpose
To determine the event-free survival (EFS) and overall survival of children with average-risk medulloblastoma and treated with reduced-dose craniospinal radiotherapy (CSRT) and one of two postradiotherapy chemotherapies.

Methods
Four hundred twenty-one patients between 3 years and 21 years of age with nondisseminated medulloblastoma (MB) were prospectively randomly assigned to treatment with 23.4 Gy of CSRT, 55.8 Gy of posterior fossa RT, plus one of two adjuvant chemotherapy regimens: lomustine (CCNU), cisplatin, and vincristine; or cyclophosphamide, cisplatin, and vincristine.

Results
Forty-two of 421 patients enrolled were excluded from analysis. Sixty-six of the remaining 379 patients had incompletely assessable postoperative studies. Five-year EFS and survival for the cohort of 379 patients was 81% ± 2.1% and 86% ± 9%, respectively (median follow-up over 5 years). EFS was unaffected by sex, race, age, treatment regimen, brainstem involvement, or excessive anaplasia. EFS was detrimentally affected by neuroradiographic unassessability. Patients with areas of frank dissemination had a 5-year EFS of 36% ± 15%. Sixty-seven percent of progresses had some component of dissemination. There were seven second malignancies. Infections occurred more frequently on the cyclophosphamide arm and electrolyte abnormalities were more common on the CCNU regimen.

Conclusion
This study discloses an encouraging EFS rate for children with nondisseminated MB treated with reduced-dose craniospinal radiation and chemotherapy. Additional, careful, step-wise reductions in CSRT in adequately staged patients may be possible.
Conclusion: This study represents the largest series of patients with average-risk MB/PNETs treated with a combination of reduced-dose RT and adjuvant chemotherapy whose intellectual development has been followed prospectively. Intellectual loss was substantial but suggestive of some degree of intellectual preservation compared with effects associated with conventional RT doses. However, this conclusion remains provisional, pending further research.
Standard-Risk: New Standard

GTR

Reduced dose CSI (23.4 Gy)

Adjuvant chemotherapy
Chemotherapy when & What?

- A range of alkylator and platinum based regimens available
- Adjuvant VCP=Adjuvant VLP
- Other effective regimens: VLCP, VC, VJPE, MICE
- When? NeoAdjuvant CT detrimental (SIOP-II) / inferior to adjuvant CT in average risk (HIT-91)
Standard Risk: Future

GTR

CSI (23.4 Gy) 18 Gy

Adjuvant chemotherapy
± HDCT
High-Risk: Standard of care

GTR

CSI (36Gy)+PF boost 19.8Gy

Adjuvant chemotherapy

Chemotherapy improves survival by 15-20% c/t RT alone historical cohorts
## High Risk trials

<table>
<thead>
<tr>
<th>High risk</th>
<th>1986–92</th>
<th>203</th>
<th>Eight drugs in 1 day preradiation and postradiation (54/36) vs vincristine, lomustine, prednisolone postradiation (54/36)</th>
<th>43 vs 63</th>
<th>0.006</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCG921</td>
<td>1996–99</td>
<td>19</td>
<td>Topotecan window preradiation (55/36–39/6) then high-dose cyclophosphamide, cisplatin, vincristine</td>
<td>84†</td>
<td></td>
</tr>
<tr>
<td>SJME'96</td>
<td>1983–93</td>
<td>15</td>
<td>Vincristine, lomustine, cisplatin postradiation (55/2/36)</td>
<td>67</td>
<td></td>
</tr>
</tbody>
</table>

CHOP/CNMC/CMCD.
High Risk: Neoadjuvant vs Adjuvant CT

• Progressive disease rates of 20-30% during neoadjuvant CT in higher M stage – (CCG-921)

• Delay in RT detrimental to long term outcome (HIT-91)

• Short neoadjuvant window (6-8 weeks) may be acceptable without any detriment
Feasibility of Four Consecutive High-Dose Chemotherapy Cycles With Stem-Cell Rescue for Patients With Newly Diagnosed Medulloblastoma or Supratentorial Primitive Neuroectodermal Tumor After Craniospinal Radiotherapy: Results of a Collaborative Study

Douglas Strother, David Ashley, Stewart J. Kellie, Akta Patel, Dana Jones-Wallace, Stephen Thompson, Richard Heideman.


Results: Fifty of the 53 patients commenced high-dose chemotherapy, and 49 patients completed all four cycles. The median length of chemotherapy cycles one through four was 28, 27, 29, and 28 days, respectively. Engraftment occurred at a median of 14 to 15 days after infusion of stem cells or autologous bone marrow. The intended dose-intensity of cyclophosphamide was 1,000 mg/m²/wk; the median delivered dose-intensity was 1,014, 1,023, 974, and 991 mg/m²/wk for cycles 1 through 4, respectively; associated median relative dose-intensity was 101%, 102%, 97%, and 99%. No deaths were attributable to the toxic effects of high-dose chemotherapy. Early outcome analysis indicates a 2-year progression-free survival of 93.6% ± 4.7% for the average-risk patients. For the high-risk patients, the 2-year progression-free survival is 73.7% ± 10.5% from the start of therapy and 84.2% ± 8.6% from the start of radiation therapy.

Conclusion: Administering four consecutive cycles of high-dose chemotherapy with stem-cell support after surgical resection and craniospinal irradiation is feasible in newly diagnosed patients with medulloblastoma/supratentorial PNET with aggressive supportive care. The early outcome results of this approach are very encouraging.
High Risk: HDCT

Surgical Resection (n=53)

Stem Cell Harvest/Topotecan window (HR only)

Radiation Therapy (n=53)

19 with high-risk (HR) disease and 34 with average-risk (AR) disease

Off study (n=3; 3 HR)
2 with progressive disease
1 ECOG > 3

HDC cycle 1 (n=50; 16 HR; 34 AR)

Off study (n=1 HR)
Grade 3 cardiac toxicity

HDC cycles 2 and 3 (n=49; 15 HR; 34 AR)

HDC cycle 4 (n=49; 15 HR; 34 AR)
4 did not receive ABMT or SCR

(HDC = high dose chemotherapy; ABMT = autologous bone marrow transplant; SCR = stem cell rescue).

High Risk: Novel approaches: radiosensitization

- CCG-99701
High-Risk: Current trials

GTR

CSI (36Gy) + PF boost 19.8 Gy ± CT

Adjuvant chemotherapy (HDCT) ± biologic therapy
Infants & Young Children (<3 yrs)

- Aim to delay, modify or possibly obviate the need for radiotherapy

- Chemotherapy alone after surgery:
  - Response rates 30-40%
  - PFS rates 22-40% at 5 years
## Infant Trials

<table>
<thead>
<tr>
<th>Protocol</th>
<th>N</th>
<th>Regimen</th>
<th>Results 5yrPFS</th>
<th>NO RT</th>
<th>Prognostic factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCG 9921</td>
<td>92</td>
<td>VCPE/VIJE</td>
<td>32%</td>
<td>83%</td>
<td>M1, Residual disease, &lt;1yr</td>
</tr>
<tr>
<td>(2006)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFOP</td>
<td>79</td>
<td>PrJ/PE/VC/HDCT</td>
<td>R0M0-29%</td>
<td>22%</td>
<td>Residual disease &gt; M1</td>
</tr>
<tr>
<td>(2005)</td>
<td></td>
<td></td>
<td>R1M0-6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R1M1-13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIT-92</td>
<td>43</td>
<td>VCJM+Itmtx</td>
<td>R0M0-82%</td>
<td>53%</td>
<td>Desmoplasia, M+, &lt;2yr</td>
</tr>
<tr>
<td>(2004)</td>
<td></td>
<td></td>
<td>R1M0-50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R1M1-33%</td>
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</tbody>
</table>
Infant & Young children

- Chemotherapy alone is effective in nondisseminated, totally resected disease
- Current trials
  - Induction CT± Intrathecal CT
  - consolidation CT(HDCT)
  - Focal conformal RT (Based on disease status)
Recurrent Medulloblastoma

- Poor prognosis
- Universally fatal till recently
- Trials of single agents or combinations with good initial response but poor long term survival
- Local relapse and chemosensitivity good prognostic factors
- HDCT promising results with 34% EFS in a CCG study with best outcome in patients with minimal residual disease pre-transplant
Novel targeted agents
## Status of Novel approaches

<table>
<thead>
<tr>
<th>Novel treatment strategy</th>
<th>Desired effect</th>
<th>Active clinical trials (agent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDCT and ASC support</td>
<td>Penetrate BBB, ↑ CNS drug level</td>
<td>COG-99702, high-risk patients, closed; COG-99703, infant patients; POG-9430, recurrent disease</td>
</tr>
<tr>
<td>IT chemotherapy</td>
<td>Prevent or treat LM disease</td>
<td>PBTC-001 (mofosfamide); PBTC-005 (busulfan); COG-P9962 (topotecan)</td>
</tr>
<tr>
<td>Radiosensitization</td>
<td>↑ RT cytotoxicity</td>
<td>COG-99701 (carboplatin/RT)</td>
</tr>
<tr>
<td>BBB disruption</td>
<td>↑ CNS drug level</td>
<td>COG-09716 (carboplatin/lombradimil)</td>
</tr>
<tr>
<td>Biologic therapy</td>
<td>Target essential tumor bioactivity</td>
<td>PBTC-002 (VEGFR TKI); closed; PBTC-003 (FTI)</td>
</tr>
<tr>
<td>Focal RT</td>
<td>↓ RT neurotoxicity</td>
<td>PBTC-001 (3-D conformal RT)</td>
</tr>
</tbody>
</table>

Abbreviations: ASC = autologous stem cell; COG = Children’s Oncology Group; FTI = farnesyl transferase inhibitor; HDCT = high-dose chemotherapy; LM = leptomeningeal; PBTC = Pediatric Brain Tumor Consortium; POG = Pediatric Oncology Group; VEGFR TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitor.
FUTURE OF MEDULLOBLASTOMA THERAPY

Surgery → Neuraxis imaging and cerebrospinal fluid

Comprehensive clinical, histopathological, and molecular staging

Tumour → Molecular and histopathological studies

Histology → DNA → RNA → Protein

Low risk → Chemotherapy and 55/18 Gy

Moderate risk → Chemotherapy and 55/35 Gy

High risk → High-dose chemotherapy with or without experimental treatment and 55/36 Gy
Team Work