MEDULLOBLASTOMA

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**Childhood Brain Tumors**

Heterogeneity/Age-Related Challenges (early diagnosis; therapeutic options)

<table>
<thead>
<tr>
<th>Tumor-Type</th>
<th>% Childhood</th>
<th>Survival 1980</th>
<th>Survival 2007</th>
<th>Survival (PFS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulloblastoma</td>
<td>20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average-Risk</td>
<td>60%</td>
<td>60%</td>
<td>80-85% (75%+)</td>
<td></td>
</tr>
<tr>
<td>Poor-Risk</td>
<td>40%</td>
<td>35%</td>
<td>60-70% (55%+)</td>
<td></td>
</tr>
<tr>
<td>Low-Grade Gliomas</td>
<td>30%</td>
<td>70%</td>
<td>80% (?)</td>
<td></td>
</tr>
<tr>
<td>High-Grade Gliomas</td>
<td>10%</td>
<td>10%</td>
<td>20% (20%)</td>
<td></td>
</tr>
<tr>
<td>Brain Stem Glioma</td>
<td>15%</td>
<td>10-20%</td>
<td>10-20%</td>
<td></td>
</tr>
<tr>
<td>Low-grade; Focal</td>
<td>20%</td>
<td>50%</td>
<td>80% (50%)</td>
<td></td>
</tr>
<tr>
<td>Diffuse</td>
<td>80%</td>
<td>5-10%</td>
<td>5-10%</td>
<td></td>
</tr>
<tr>
<td>Ependymomas</td>
<td>10%</td>
<td>40%</td>
<td>60-70% (50%)</td>
<td></td>
</tr>
</tbody>
</table>

*Improved Quality-of-Life*
Medulloblastoma

- Most common childhood malignant brain tumor
- Tumor with greatest “apparent” improvement in survival
  - stepwise
  - effect of re-classification
  - challenge of quality-of-life of survivors
- Transition in care: molecular genetics
  - understanding
  - stratification
  - management
Childhood Brain Tumors

Critical Issues:

- Has there been a “significant” increase in understanding the neurobiology, genetics or causation of childhood brain tumors?
- Have these new understandings resulted in different or better management?
- Has there been an improvement in survival?
- Has there been an improvement in quality of life of survivors?
Medulloblastoma

WHO Classification

- Medulloepithelioma
- Ependymoblastoma
- * Medulloblastoma
  - Desmoplastic
  - Large cell (\textit{? anaplastic})
  - Melanotic
- Supratentorial primitive neuroectodermal
  - Neuroblastoma
  - Ganglioneuroblastoma
- AT/RT

* Genetically different (cytogenetics: molecular genetics)
Medulloblastoma

**Cellular origin**
- No longer an intellectual exercise alone
- May be key to stratification/management

**For decades known**
- Histologically heterogeneous
- ? Role of heterogeneity in outcome
  - differentiated (*Rorke*)
  - large-cell / anaplastic (*Burger*)
  - light → immunohistochemistry → molecular genetics
Medulloblastoma

• ? Multipotential precursors

• Location of progenitor in cerebellum
  - cerebellum has two germinal zones
    • ventricular (? multipotential)
    • external granular layer (? restricted)

• ? restricted neuronal precursors (neuroblasts)
VZ (multipotent stem cells)

E13-E17

rhombic lip (GCPs)

EGL

E18-P14

molecular layer

Purkinje cell

IGL

WM

E13-E17

WM

VZ

IGL

EGL

Adult
Medulloblastoma

Surgery

- Not straightforward
- Key element
  - ? for all
  - Extent of resection associated with outcome

- “What is” role in disseminated patients
- Sequelae
  - Direct Brain Damage
  - Posterior-fossa mutism
Figure 9C
Eligible Randomized Patients
PF-PNET & MO: PFS

Yrs Post On Study

Probability

< 90 %

>= 90 %
Medulloblastoma

Posterior-fossa mutism

- Delayed onset of mutism associated with hypotonia, cerebellar dysfunction (truncal and appendicular), emotional lability, supranuclear palsies (eyes, swallowing), etc…

- Incidence
  . Center dependent
  . 25% nationally

- 50% ? permanent sequelae; intellectual

- Vermian damage (?)

- Increased incidence or increased recognition
Medulloblastoma

Stratification

- Clinically/Postoperatively since early 1990’s
  A. Dissemination
  B. Resection
  (C. Age)
  (D. Histology)

- Two Risk Groups
  A. Average – RT alone; RT + chemo (60-70%)
  B. Poor or High – RT plus chemo (30 – 40%)

- Infants / Young Child
  A. Separately stratified
  B. What defines an “infant”
Medulloblastoma: Basic (1980’s/1990’s) Stratification

- Disease extent: Localized, Disseminated
- Age: Older; \( ? > 3 \) years, Younger
- Extent of resection: Total/?Near total, Partial/Biopsy
- Location: Posterior-Fossa, Other
A9961: Eligibility

400 patients reviewed

334 (79%) eligible
32 (7.6%) ineligible

- 26 disseminated ± residual disease
- 6 other

55 (13%) unevaluable
A9961 Event-Free Survival from Study Entry

Overall: p=0.006
Eligible vs. Ineligible: p=0.002
Eligible vs. Unevaluable: p=0.15

n=334
n=55
n=32
Medulloblastoma

Large cell/anaplastic variant

- Defined as light microscopy findings of pleomorphic nuclei, prominent nuclei, abundant cytoplasm, large areas of necrosis, high-mitotic activity, high apoptosis (*apoptotic lakes*), cellular atypia; background of “anaplastic” tissue

- Related to large cell variant (*same*)

- Subjective

- Does not clearly incorporate mitotic index measures

- Modified by ? Severe; focal; diffuse, etc…
Event-Free Survival for A9961/99701 by Anaplasia

- No Anaplasia (n=339)
- Anaplasia (n=74)

Probability vs Years from study entry

p=0.0083
Survival: ErbB2 Protein Expression

Gilbertson RJ et al, Cancer Res 1997

\[ p = 0.0039 \]
Survival: cMYC RNA Expression

Grotzer MA et al, Clin Cancer Res 2001

B

Survival Probability

0.00 0.25 0.50 0.75 1.00

Low MYC (n = 13)

High MYC (n = 13)

p = 0.018

Years Since Diagnosis

0 2 4 6 8 10
Survival: RNA Expression Profile

Predictor genes: Cell cycle, ribosome regulation

Pomeroy SL et al, Nature 2002
Biologic Prognostic Markers:

Medulloblastoma

Favorable prognosis

Unfavorable prognosis

**Disease:**
- Local
- Metastatic

**Histology:**
- Desmoplastic
- Large cell/Anaplastic

**Genotype:**
- PTCH mutation?
- cMYC amplification

**Expression:**
- TRKC
- ErbB2, cMYC, RNA profile: cell cycle, ribosome metastasis
Medulloblastoma

Stratification Issues

- With better neuro-imaging, more average risk → high
  - improves outcome of average-risk
  - improves outcome of high-risk

- Neuroimaging not as standardized

- Does not account for impact of therapy

- Does not incorporate molecular marker
  - ? replace/enhance clinical

- Intermediary risk group
Medulloblastoma

Radiotherapy

- Backbone of effective treatment

- Necessary evil of craniospinal
  - cognitive sequelae
  - endocrinologic sequelae

- Can it be used alone?
  ? adults

- Can local RT be used?
  ? subsets
  ? infant/young child

- New techniques make it less toxic/effective
  ? conformal boost
  ? proton beam

- CSRT dose reduction
Medulloblastoma

X-RAYS

PROTONS
CCG-923/POG 8631: Low Stage Medulloblastoma Reduced-Dose RT

Treatment Schema

- Randomized 3600 cGy CSRT vs. 2340 cGy CSRT
- No chemotherapy

Baseline and yearly neurocognitive, endocrinologic assessment
1. POG 8631/CCG 923 – All Eligible Pt
Event–Free Survival

Years Followed

LEGEND

--- Standard

--- Reduced
Medulloblastoma

Radiotherapy / Chemotherapy

- Chemotherapy (during/post RT) associated with 20-30% improvement in EFS / S
  - No randomized comparisons

- Chemotherapy standard adjuvant in children

- Sequencing of major importance
  - best EFS/S if RT not delayed
  - ? Makes up for reduced CSRT
Medulloblastoma Study: RT plus CCNU, VCR, and CPDD

**Treatment Protocol**

RT: 3600 cGy CSRT

5400 cGy Total Local \{ 180 cGy daily \}

(2340 cGy CSRT *in younger*) \{ fractions \}

Chemo Rx: VCR (1.5 mg/m²) weekly during RT

8 6-week cycles of:

- CPDD (68 mg/m²) x 1
- CCNU (75 mg/m²) x 1
- VCR (1.5 mg/m²) x 3
A Phase III Prospective Randomized Study of Craniospinal Radiotherapy Followed by One of Two Adjuvant Chemotherapy Regimens (CCNU, CDDP, VCR or CPM, CDDP, VCR) in Children with Newly-Diagnosed Average-Risk Medulloblastoma

A Phase III Intergroup (CCG/POG → COG) Study

Roger J. Packer, MD  (Chair)
Amar Gajjar, MD  (Vice-Chair)
Richard Sposto  (Statistician)
A9961 Event-Free Survival from Study Entry

Percent Event-Free

RegA  RegB

85 +/- 3%
83 +/- 3%

Time (years)

p=0.65

50%  60%  70%  80%  90%  100%
A9961 Survival from Study Entry

89 +/- 2% for A and B

p=0.85
Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma: long-term results from a prospective, multicentre trial – SJMB 96

Amar Gajjar, M.D.
St. Jude Children’s Research Hospital
Panel: High-dose chemotherapy protocol (one cycle)

Day -4—Intravenous doses of 75 mg/m² cisplatin and 1.5 mg/m² (maximum 2 mg) vincristine
Days -3 and -2—Intravenous dose of 2 g/m² cyclophosphamide; continuous infusion of mesna
Day -1—Hydration

Day 0—Infusion of peripheral blood or bone-marrow progenitor cells (peripheral-blood stem-cell dose $2 \times 10^6$ CD34 cells/kg)
Day +1—Subcutaneous or intravenous dose of 5 μg/kg filgrastim per day, until absolute neutrophil count reaches $\geq 2 \times 10^9$/L on 2 consecutive days after expected nadir of absolute neutrophil count
Day +6—Intravenous dose of 1.5 mg/m² vincristine
SJMB 96 – 5 yr risk stratified event free survival

Figure 1: Event-free survival for average-risk and high-risk patients

Gajjar et. al., Lancet Oncology, 2006
SJMB 96 – Treatment Schema compared to standard chemotherapy regimens

Figure 3: Comparison of SJMB-96 protocol for average-risk and high-risk patients with protocols used in contemporary national clinical trials

Gajjar et. al., Lancet Oncology, 2006
The diagram shows the progression-free survival (PFS) for two arms of a clinical trial. The x-axis represents the time in years, and the y-axis represents the probability.

- **Arm I** (n=39): 0.62 (± 0.09)
- **Arm II** (n=36): 0.84 (± 0.08)

The p-value for the difference between the two arms is 0.03, indicating a statistically significant difference in PFS between the two arms.

Arm I = Sandwich chemotherapy
Arm II = Maintenance chemotherapy
Medulloblastoma

Chemotherapy Issues

• What is “best” adjuvant regimen for average-risk?
  - CCNU, CPDD, VCR
  - CYCLO, CPDD, VCR
  - CYCLO, CPDD, VP16, VCR plus PSRC
  - Others

• What is “best” adjuvant regimen for high/poor-risk?

• Toxicity
  - ? additive with RT (growth, Q-O-L)
  - ? Hearing (CPDD ± RT)
  - ? Neuropathy (VCR)
  - ? Hormonal (sterility)

• Infants/Young Child
# Pattern of Relapse

<table>
<thead>
<tr>
<th>Study</th>
<th>SIOP/UKCCSG</th>
<th>COG</th>
<th>COG</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNET 3</td>
<td>9892</td>
<td>A9961</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SIOP/UKCCSG</th>
<th>COG</th>
<th>COG</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSRT-3500</td>
<td>CSRT-2340</td>
<td>CSRT-2340</td>
<td></td>
</tr>
<tr>
<td>+ ChemoRx</td>
<td>+ ChemoRx</td>
<td>+ ChemoRx</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relapse</th>
<th>SIOP/UKCCSG</th>
<th>COG</th>
<th>COG</th>
</tr>
</thead>
<tbody>
<tr>
<td>53/179</td>
<td>15/65</td>
<td>60/421</td>
<td></td>
</tr>
</tbody>
</table>

| PF only       | 12 (22.6%)  | 2 (14%)  | 11 (12%) |
| PF+distant    | 26 (49%)    | 9 (64%)  | 15 (25%) |
| Distant only  | 15 (28.3%)  | 3 (21%)  | 29 (48%) |

| Component disseminated | 77% | 85% | 73% |
Medulloblastoma

Average-risk (non-disseminated) outcome

• Acceptable 5-year EFS → 80% (? 90%)
• Different protocols, primarily toxicity
• Differences if chemotherapy used after RT
  - Pre-RT chemo, to date, inferior results
• Pattern of relapse, predominantly disseminated ± local
• Q-O-L deficits complex etiology
• Next steps balance survival versus reduced sequelae
Pilot Study of 1800 cGy CSRT plus Chemotherapy (CCNU, VCR and CPDD)

- Entered 10 patients between 18 months and 5 years
- All nondisseminated posterior fossa medulloblastoma
- 3 early failures
  - 1 disseminated
  - 2 local and disseminated
- No other failures
- 5-year survival 70 +/- 20%
- IQ at 3 years approximated 100 (no documented fall)
Limited Target Volume Boost Irradiation and Reduced Dose Craniospinal Radiotherapy and Chemotherapy in Standard Risk Medulloblastoma A Phase III Double Randomized Trial
Children’s Oncology Group
Average Risk Medulloblastoma
ACNS0331 Proposed Schema

Age 3-7 years
- CSRT 23.4Gy
- IF boost 54Gy
- PF boost 54Gy

Age 8-21 years
- CSRT 23.4Gy
- IF boost 54Gy
- PF boost 54Gy

Weekly vincristine during XRT
Outcome for patients with metastatic (M2–3) medulloblastoma treated with SIOP/UKCCSG PNET-3 chemotherapy

Fig. 1. Overall survival (OS) and Event-free survival (EFS).

Table 3
Comparisons of outcome for M2–3 medulloblastoma in different multicentre studies

<table>
<thead>
<tr>
<th>Study (with stages included)</th>
<th>Reference</th>
<th>Number of patients</th>
<th>Dates of recruitment</th>
<th>Outcome at 3 years</th>
<th>Outcome at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIOP 81 M2 + M3</td>
<td>[5]</td>
<td>29</td>
<td>1964–1989</td>
<td>PFS 45%</td>
<td>PFS 40%</td>
</tr>
<tr>
<td>Present study M2 + M3</td>
<td>This study</td>
<td>68</td>
<td>1992–2000</td>
<td>OS 80.0%, EFS 33.7%</td>
<td>OS 43.9%, EFS 34.7%</td>
</tr>
</tbody>
</table>

FOG, Pediatric Oncology Group; SIOP, International Society of Pediatric Oncology; CCG, Childhood Cancer Group.
SJMB 96 – 5 yr risk stratified event free survival

Figure 1: Event-free survival for average-risk and high-risk patients

Gajjar et. al., Lancet Oncology, 2006
**POG 9031 Schema**

<table>
<thead>
<tr>
<th>Randomize</th>
<th>7 Wks VP-16/Cisplatin</th>
<th>XRT</th>
<th>28 Wk Vincristine/Cyclophosphamide</th>
</tr>
</thead>
</table>

**XRT**
- Craniospinal irradiation (CSI) 35.2 - 44 Gy
- Posterior Fossa boost 53.2 - 56.8 Gy

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*Figure 1: POG 9031 Treatment Schematic*
Medulloblastoma

Poor-risk (disseminated) outcome

• Present 5-year EFS survival 60 – 70%
• Different protocols using high-dose RT plus chemotherapy show best survivals
• Concern over quality-of-life issues have not been fully addressed.
• Dissemination does not mean disease relapse
• Probably some subsets resistant to therapy
Medulloblastoma: Poor-risk (concept)

- Eligibility:
  - 3 years or greater
  - All M+ medulloblastoma
  - All supratentorial medulloblastomas
  - All ? Subtotally resected MO

- Treatment (Double randomization)
  - RT ± carboplatin daily
  - All Cyclo or CCNU/CPDD/VP16/VCR post RT chemo
  - ± Retinoic Acid
A9961: Follow-up

379 eligible subjects

- 309 without relapse (7.3 median Flu)
  - 258 in active follow-up
  - 11 secondary tumors
  - 40 ?L.T.F.U.
- 70 relapses
  - 49 within year 2
  - 8 year 5 or after
- Of relapses
  - 36 died within 1 year
  - 45 died within 2 years
  - 7 alive
  - 14% long term survivors
A9961 SMN

11 SMN noted

Time post initiation treatment

- Years 3-5
  - 1 GBM (cerebellum)
  - 1 T-cell leukemia
  - 1 soft tissue
  - 1 basal cell

- Years 5+
  - 1 GBM temporal lobe
  - 2 myeloplastic
  - 1 osteosarcoma
  - 1 Pilocytic (cerebellum)
  - 1 thyroid carcinoma
Medulloblastoma

• Addition of chemotherapy (post RT) has improved survival

  *Caveat:* Some recent “improvements” may be more apparent than real, as reclassification results in more favorable “average-risk” and less extensive / aggressive “poor-risk” subsets

• Biologic advances impressive

  *Caveat:* Not changed stratification in “real-time” yet and new targets not yet fully validated nor exploited

• Outcome not clearly better

  *Caveat:* Reduction of CSRT beneficial, but still significant late sequelae; effect of post-fossa mutism needs to be better assessed
Medulloblastoma

Infants

- No consistent definition of who is too young for RT *(especially CSRT)*
- Non-randomized comparisons suggest improved survival with more aggressive chemotherapy
  - Primarily in non-disseminated
  - Removal of AT/RT included in earlier studies
  - Possible replacement by toxic therapies to the developing nervous system
Chemotherapy for Infants: Pediatric Oncology Group Experience

<table>
<thead>
<tr>
<th>Eligibility:</th>
<th>All biopsy proven malignant gliomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs:</td>
<td>Cyclophosphamide 65 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Vincristine 0.065 mg/kg x 2</td>
</tr>
<tr>
<td></td>
<td>Cisplatin 4 mg/kg</td>
</tr>
<tr>
<td></td>
<td>VP 16 6.5 mg/kg</td>
</tr>
<tr>
<td>Cycles:</td>
<td>Cyclo/VCR x 2</td>
</tr>
<tr>
<td></td>
<td>CPDD/VP16</td>
</tr>
<tr>
<td>Week 1</td>
<td>Week 3</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Methotrexate (2 mg/day, intraventricular),</td>
<td>Methotrexate (2 mg/day,</td>
</tr>
<tr>
<td>day 1–4</td>
<td>intraventricular), day 1–2</td>
</tr>
<tr>
<td>Cyclophosphamide (800 mg/m² of body-</td>
<td>Methotrexate (5 g/m², intravenous), 24 hr</td>
</tr>
<tr>
<td>surface area/day, intravenous), day 1–3</td>
<td></td>
</tr>
<tr>
<td>Vincristine (1.5 mg/m², intravenous), day 1</td>
<td>Vincristine (1.5 mg/m², intravenous), day 1</td>
</tr>
</tbody>
</table>

* One two-month cycle of intraventricular and systemic chemotherapy consisted of four treatments. The second and third cycles of chemotherapy were started at weeks 10 and 19, respectively. Treatment was finished if patients were in complete remission after three cycles of chemotherapy.
Infant Medulloblastoma

HIT - 1992

- 3 cycles of Cyclo/VCR; HDMTX, Carbo/VCR/IT
  (Greater than 18 months and not CCR → CSRT/MTX)

- 43 patients (23 desmoplastic)
  . Mo, Total 17  (82%)
  . Mo, Subtotal 14  (56%)
  . M+, Total 13  (33%)

- Overall 5-year PFS  71% (w/o RT)
  . Desmoplastic  85%
  . Classical  34%
Figure 2. Progression-free Survival among 23 Children with Classic and 20 Children with Desmoplastic Medulloblastoma.
Figure 3. Effect of Treatment on Neurocognitive Functions.

The results of IQ tests are expressed as T scores and IQ points. Neurocognitive deficits in children treated with intraventricular and systemic chemotherapy were less pronounced than the deficits in children receiving radiotherapy. Six children received radiotherapy as salvage therapy after systemic and intraventricular chemotherapy, 11 received systemic chemotherapy and radiotherapy but no intraventricular methotrexate, 14 received systemic chemotherapy and intraventricular methotrexate, and 3 received systemic chemotherapy but no intraventricular methotrexate or radiotherapy. There were 23 children in the control group. CPM denotes Colored Progressive Matrices test, VMI Developmental Test of Visual-Motor Integration, and K-ABC Kaufmann-Assessment Battery for Children.
Eligibility:
- Age: 8 - 36 months
- Stage: \( M_0 \)

Treatment:
- 4 cycles induction chemotherapy (Cyclo, CPDD, VP16, VCR)
- Second look surgery
- Involved conformal RT
- Maintenance chemotherapy
Infant Medulloblastoma

Hypothesis:

- Aggressive chemotherapy (HD ± ITMTX) can result in 70% PFS (?OS) in Mo

Plan:

- Average-Risk (Mo, Total)
  - HITSKK (± ITMTX) vs COG 99703
  - No RT
- ? Over treatment of Desmoplastic
- In high-risk: If Mo, Subtotal - ? add conformal RT
- In high-risk: If M+ - ?
Medulloblastoma

Infants

- MOPP alone, some survivors
- In retrospect, Baby POG used chemo plus CSRT (*at age 3*) and overall poor results
- Encouraging results from:
  - German protocol without MTX (HIT-SKK)
  - German protocol with MTX (*IV and IT*)
  - Early COG-99703 high-dose plus PSCR
- Biology probably the determinant
- Role of RT to be defined
- Little progress in disseminated disease
PFS Improvement Predominantly M0 MB and sPNET

3-Yr EFS All Resections M0 MB%
Childhood Infant Malignant Tumors

- Separation of AT/RT from medulloblastoma a major advance

- Separation of nodular/desmoplastic (? external granular layer lineage) from other medulloblastomas may improve quality of life of subset of infants

- Primary improvement in the subset of non-disseminated / ? totally resected medulloblastoma
Medulloblastoma

- 65 – 70% of all children survive; many cured

- Multiple Issues
  - Cognition
  - Hormonal
  - Neurologic Function
  - Secondary Tumors
  - Obesity
  - Quality-of-Life
  - Independence in future
    - job
    - family
    - psychosocial
Medulloblastoma

*Childhood Cancer Survivor Study*

- 10-20% have neurologic dysfunction
  - ataxia
  - dysmetria
  - weakness
- 10-20% have neurosensory dysfunction
  - visual problems
  - dizziness
  - tinnitus
- Not clear if this is improving with “modern” treatment
  - CPDD toxicity now being seen
  - Posterior fossa mutism
# Metastasis: RNA Expression

## M0 vs M+ Tumors

<table>
<thead>
<tr>
<th>Protein</th>
<th>Non-metastatic Tumors</th>
<th>Metastatic Tumors</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAP-1</td>
<td>0.94 ± 0.06</td>
<td>0.93 ± 0.06</td>
<td>0.625</td>
</tr>
<tr>
<td>NOS-1</td>
<td>1.12 ± 0.12</td>
<td>1.13 ± 0.13</td>
<td>0.789</td>
</tr>
<tr>
<td>gapdh</td>
<td>0.95 ± 0.05</td>
<td>0.96 ± 0.06</td>
<td>0.517</td>
</tr>
</tbody>
</table>

**Down in M+**

- Metastasis: Reduced expression of GAP-1 in M+ tumors compared to M0.

**Up in M+**

- Metastasis: Increased expression of NOS-1 in M+ tumors compared to M0.

**RAS/MAPK**

- Activation of RAS/MAPK pathway in M+ tumors.

**PDGFRA**

- Upregulation of PDGFRA in M+ tumors.

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MacDonald TJ et al, Nat Genet 2001
“Metastatic Pathway”

RTK: ErbB2, PDGFR

RAS/MAPK
Summary of Tumor Cell Targets

(Gefitinib or Lapatinib)

Zarnestra
Medulloblastoma

Incorporation of biologic agents

• Frustratingly slow

• Which patients *(biologic selection)*

• How
  - alone
  - multiple biologic agents
  - with chemotherapy

• How do you choose agents
  - single agent *(static)*

• Retinoic acid first in randomized trials
Medulloblastoma

Future – Many Challenges

- Even with “standard-conventional” therapy, many issues
  - consistency of basic neuro-imaging
  - consistency of histologic diagnosis
  - consistency of stopping rules for use of chemotherapy
  - how do we approach a 25% incidence of surgical complications
Medulloblastoma

Future – Many Challenges (continued)

• Quality-of-Life/sequelae
  - Molecular identification of those at highest risk (RT injury)
  - Cost effective way to follow patients for cognitive/psychosocial sequelae
  - Remediation of what we now cannot prevent
Medulloblastoma

Future – Many Challenges (continued)

• Rapid incorporation of molecular genetic findings into standard care
  - Identify those at risk and modify treatment accordingly
  - For some, no RT at all
  - For some, possibly less chemotherapy
  - Can we avoid CSRT for other?

• Incorporation of biologic agents into therapy
  - Which agents / which pathways
  - Therapy biologically based on ? type of medulloblastoma
  - Which cocktails