CHEMOTHERAPY OVERVIEW

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“Poisons in small doses are the best medicines; and the best medicines in too large doses are poisonous”

William Withering (1741 - 1799)
A chemotherapeutic agent is a substance that can target and selectively kill transformed cells.
Principles of Cancer Treatment

Local Therapy

- Surgery
- Radiation therapy

Systemic Therapy

- Chemotherapy
- Hormonotherapy
- Immunotherapy
- Targeted therapy
Biochemistry

Cytotoxic chemotherapy drugs damage the cancer cells:

- Interfering with the synthesis of the precursor DNA
- Chemically interacting with the DNA itself
Fundamental Approaches to Cancer Chemotherapy

- **G_0**: Cell rests
- **G_1**: Cell enlarges and makes new proteins
- **G_2**: Cell prepares to divide
- **S**: Cell replicates its DNA
- **M**: Cell divides (Mitosis)
Chemotherapy: Cell Cycle

- **DNA**
  - De Novo Synthesis
  - Salvage Pathway
  - Purines
  - CMP
  - dCMP
  - dTMP
  - FH2
  - FH3
  - Dactinomycin
  - Doxorubicin
  - Daunomycin
  - Idarubicin
  - Topoisomerase-mediated breaks
  - Intercalation
  - Free Radical Damage
  - Alkylation

- **RNA**
  - Mercaptopurine
  - Thioguanine
  - Folinic Acid
  - Asparaginase

- **Protein**
  - Tubulin
  - Vincristine
  - Vinblastine
  - Paclitaxel

- **Drugs**
  - Fluorouracil
  - Methotrexate
  - Mercaptopurine
  - Thioguanine
  - Fluorouracil
  - Methotrexate
  - Mercaptopurine
  - Thioguanine
  - Mechlorethamine
  - Cyclophosphamide
  - Ifosfamide
  - Melphalan
  - Carboplatin
  - Cisplatin
  - Nitrosourea
  - Busulfan
  - Dacarbazine (Temodar)
  - Procarbazine
  - Doxorubicin
  - Daunomycin
  - Idarubicin
  - Bleomycin
  - Dactinomycin
  - Doxorubicin
  - Daunomycin
  - Idarubicin
  - Etoposide
  - Teniposide
  - Topoisomerase-mediated breaks
  - Cytarabine
  - Alkylation
**Blood Brain Barrier**

• Drugs which penetrate the BBB

  Carboplatin  
  BCNU/CCNU  
  Etoposide (VP16)  
  **Temozolomide**  
  Cytarabine  
  Tamoxifen  
  Procarbazine  
  Vincristine  
  Methotrexate

**Small Molecules**

  Cediranib (Pan VEGF)  
  Erlotinib
Glioblastoma
Anaplastic Astrocytoma
Anaplastic Oligodendrogliomas
Mixed Astrocytomas
some low grade gliomas
Nitrosoureas

- **Carmustine (BiCNU)** Bifunctional alkylating agent, IV administration
- **Lomustine (CeeNU)** monofunctional alkylating agent, oral administration
- **Streptozocin (zanosar)**
- **Fotemustine**
- **Bendamustine (CSMC Trial)**
Carmustine and lomustine are lipid soluble drugs: penetrate the nervous system (treat central nervous system malignancies, *optic and neurological complications were reported*).

- Used also for treating malignant lymphomas, melanomas and some GI tumors.
- Myelosuppression is the dose-limiting toxicity.
- Cause nausea and vomiting.
- Long term use of *carmustine* may cause *pulmonary toxicity*.
Gliadel wafers?

• Phase 3 Trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma (Westphal- Neuro-Oncology, 2004)

• Biodegradable polyanhydride copolymer containing BCNU; implanted on the surface of surgical resection cavity (usually up to 8 wafers); release BCNU slowly over a 2-3 week period

• Median overall survival: 13.9 months (vs 11.6 months) p<0.05

• FDA approved
Temozolomide (Temozodar)

3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-as-tetrazine-8-carboxamide
Temozolomide (Temodar)

Mechanism of Action:

• Temozolomide is not directly active but undergoes conversion to MTIC when it passes through the blood brain barrier.

• Active metabolite that methylates DNA at guanine’s O6 position

Metabolism and Elimination:

Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC.

* So there are few drug interactions!
What to expect from TMZ?

• The **most commonly used drug**

• Well tolerated

• Fatigue, N/V, myelosuppression, headaches

• Regimens:
  - 150-200 mg/m² for 5 days every 28 days (? # cycles)
  - 75 mg/m² while on RT, wait 4 weeks then re-start with regimen above
What to expect from TMZ?

- Phase III trial chemoradiation:

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>TMZ/RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>12.1</td>
<td>14.6</td>
</tr>
<tr>
<td>2-yr survival</td>
<td>10%</td>
<td>26%</td>
</tr>
<tr>
<td>HR [95% C.I.]</td>
<td>0.63 [0.52-0.75]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Graph:**
- Median survival for RT and TMZ/RT treatments are shown over time, with TMZ/RT showing a statistically significant improvement in survival over RT.
Median overall and 2-year survival according to *methylguanine methyltransferase* promoter status (MGMT) – indirect measure of DNA Repair

<table>
<thead>
<tr>
<th>MGMT promoter status</th>
<th>Radiotherapy</th>
<th>Radiotherapy + temozolomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypomethylated</td>
<td>11.8</td>
<td>12.7</td>
</tr>
<tr>
<td>Hypermethylated (Less DNA Repair)</td>
<td>15.3</td>
<td>21.7</td>
</tr>
<tr>
<td>2-y survival (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypomethylated</td>
<td>&lt;2.0</td>
<td>13.8</td>
</tr>
<tr>
<td>Hypermethylated</td>
<td>22.7</td>
<td>46.0</td>
</tr>
</tbody>
</table>

1st MRI after concomitant treatment

- Enlarged lesion (50 pts)
- Stable or no lesion (53 pts) Non PD

Continue TMZ

2nd MRI after (3 months) concomitant treatment in enlarged lesion (50 pts)

- Stable or reduced psPD 32 pts (64%)
- Further progression ePD 18 pts (36%)

Continue TMZ
Stop TMZ

Methylated MGMT
- 21 (66%)
- 2 (11%)
- 13 (25%)

Unmethylated MGMT
- 11 (34%)
- 16 (89%)
- 40 (75%)

P = 0.0002

MRI findings, outcomes and MGMT status of patients

Temozolomide Rechallenge in Recurrent Malignant Glioma by Using a Continuous Temozolomide Schedule
The “Rescue” Approach

James R. Perry, ws  
Philippe Rizk, ws  
Rosemary Cashman, ws  
Meredith Morrison, ws  
Tim Morrison, ws

1 Cella Family Brain Tumor Research Unit, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada.  
2 BC Cancer Agency, Vancouver, British Columbia, Canada.  
3 Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania.

BACKGROUND. Despite advances in first-line therapy, there are few data on treatment of glioblastoma multiforme (GBM) at recurrence. Temozolomide (TMZ) is well tolerated and may have activity despite prior TMZ exposure if novel dose schedules are used.

METHODS. The authors reviewed their experience with a continuous TMZ schedule (50 mg/m² daily), given at progression after conventional 5-day TMZ. Patients were reported in 3 groups: 1) GBM after progression on conventional TMZ; 2) GBM at first recurrence after completion of standard concomitant and adjuvant TMZ; and 3) patients with other anaplastic gliomas at second relapse on conventional TMZ.

RESULTS. In Group 1, 21 patients with a median age of 54 years (range, 35 years-86 years) received a median of 3 cycles (range, 2-12 cycles) of continuous TMZ at 50 mg/m². Overall clinical benefit (complete response, partial response, and stable disease) was 67%, with 6-month progression-free survival (PFS) of 17%. In Group 2, 14 patients with GBM, median age 52 years (range, 38 years-62 years) received continuous TMZ at progression after initial TMZ/radiotherapy (RT) and adjuvant TMZ. The median interval after adjuvant TMZ was 5 months (range, 2 months-10 months). A median of 3 cycles of TMZ was given, and 6-month PFS was 57%. In Group 3, 16 patients with a median age of 53 years (range, 44 years-56 years) received continuous TMZ; 2 partial responses and 6 with stable disease were seen, with a 6-month PFS of 43%. Toxicities were mild and well tolerated; lymphopenia was common but no serious opportunistic infections were identified.

CONCLUSIONS. Although retrospective, our results demonstrate that continuous daily administration of TMZ is an active regimen despite prior TMZ therapy. The excellent tolerability of this regimen may allow future combination with other alkylating agents or with novel therapies. Cancer 2006;113:2152-7. © 2006 American

Alternative Temozolomide Dosing
• 75 mg/M2 21 days/7 days off
• 50 mg/M2 daily
• 200 mg/M2 7 days on 7 days off
(150 mg/M2 7 days on 7 days off)
Twice daily dosing

Temozolomide Rechallenge Response Rates as High as 47%
Irinotecan (CPT-11)

- Used to treat metastatic carcinoma of colon and rectum
- Severe diarrhea is the dose-limiting toxicity (dehydration + electrolyte imbalance)
Irinotecan
Mechanism of Action

- Interfere with the activity of Topoisomerase I (impairs binding of DNA) Resulting in DNA damage

- **Irinotecan** - a prodrug that is metabolized to an active Top I inhibitor, SN-38

- Big Side Effect - Diarrhea
Etoposide phosphate (VP-16)

Mechanism of Action

• An inhibitor of the enzyme Topoisomerase II
• Used to treat Ewing’s Sarcoma, Lung Cancer, Testicular Cancer, Lymphoma, Leukemia
• Derived from a toxin found in the American Mayapple
Carboplatin

Its effect is equal cisplatin in ovarian carcinoma

Used in treatment of lung, head and neck tumors

Carboplatin is cleared renally and lacks renal toxicity

Causes more myelosuppression than cisplatin
Molecularly targeted therapy for Malignant Glioma
The mantra...

- Solid tumors need blood vessels to grow.
- Angiogenesis is the process by which new vessels sprout from existing vessels.
- VEGF drives angiogenesis.

Therefore, inhibiting VEGF stops tumor growth.
## Angiogenesis inhibitors: Selected drugs...

### Anti-VEGF ligands
- Bevacizumab (Avastin)
- Aflibercept (VEGF-Trap)

### Target
- VEGF-A
- VEGF-A/B, PIGF

### Receptor Tyrosine Kinase Inhibitors
- Cediranib, AZD2171
- Dasatinib (Sprycel)
- Pazopanib, GW786034
- Sorafenib (Nexavar)
- Sunitinib (Sutent)
- Vandetanib (Zactima)
- Vatalanib, PTK787/ZK222584
- Tandutinib, MLN 518

### Target
- VEGFR, PDGFR, c-Kit
- PDGFR, Src, Bcr-Abl
- VEGFR, c-Kit
- VEGFR, PDGFR, c-Kit, Raf
- VEGFR, PDGFR, c-Kit, FLT-3
- VEGFR, EGFR, RET
- VEGFR, PDGFR, c-Kit
- VEGFR, c-Met

### Others
- Cilengitide, EMD121974
- Enzastaurin
- Metronomic chemotherapy
- Thalidomide, lenalidomide

### Target
- αvβ3 and αvβ5 integrins
- PKC-β and Akt
- Tumor endothelium
- Multiple including FGF
Avastin (Bevacizumab)
FDA Approved – May 5th 2009

- Humanized monoclonal antibody that binds to and inhibits VEGF-A.
- VEGF secreted by glioma cells acts by paracrine mechanisms upon endothelial cells in the vicinity of the tumor, resulting in endothelial cell proliferation, survival, and migration.
- The level of VEGF expression in gliomas correlates with blood vessel density, degree of malignancy, and prognosis.
- Approved for Single Agent Usage.
Bevacizumab vs. Bevacizumab/CPT11

Phase II, open-label, multicenter, randomized,
- 167 pt’s randomized to either arm at recurrence (all upfront Temodar)
- every other week for up to two years (104 weeks)
- Hemorrhage occurred in 3 participants
<table>
<thead>
<tr>
<th></th>
<th><strong>Avastin</strong></th>
<th><strong>Avastin/ CPT11</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total = 167</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6 Month PFS</strong></td>
<td>36 %</td>
<td>51 %</td>
</tr>
<tr>
<td><strong>Tumor Response Rate</strong></td>
<td>21% (18/85)</td>
<td>34% (28/82)</td>
</tr>
<tr>
<td><strong>MST</strong></td>
<td>8.2 Month</td>
<td>8.7 Months</td>
</tr>
</tbody>
</table>
Pre & Post Avastin: An Example

**PRE**

- $K_{\text{trans}}$
- fBV
- rCBV

**POST**

- fBV
- rCBV
### VEGF inhibitors: Selected trials...

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Diagnosis</th>
<th>Sponsor</th>
<th>Site</th>
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</thead>
<tbody>
<tr>
<td>Aflibercept</td>
<td>II</td>
<td>Recurrent MG</td>
<td>NCI</td>
<td>NABTC</td>
</tr>
<tr>
<td>Aflibercept, TMZ + RT</td>
<td>I</td>
<td>New GBM; recurrent MG</td>
<td>NCI</td>
<td>NABTC</td>
</tr>
<tr>
<td>Bev</td>
<td>II</td>
<td>Recurrent MG</td>
<td>Genentech, S-P</td>
<td>BTIC/CEDARS</td>
</tr>
<tr>
<td>Bev + bortezomib</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>Genentech</td>
<td>Duke</td>
</tr>
<tr>
<td>Bev + erlotinib</td>
<td>II</td>
<td>Recurrent MG</td>
<td>Genentech</td>
<td>Duke</td>
</tr>
<tr>
<td>Bev + erlotinib + RT</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>Genentech</td>
<td>Duke</td>
</tr>
<tr>
<td>Bev + TMZ or etoposide</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>Genentech</td>
<td>Duke</td>
</tr>
<tr>
<td>Bev + TMZ + Erlotinib + RT</td>
<td>II</td>
<td>New GBM</td>
<td>Genentech</td>
<td>BTIC/CEDARS</td>
</tr>
<tr>
<td>Bev + TMZ after RT</td>
<td>II</td>
<td>New GBM</td>
<td>Genentech</td>
<td>U Chicago</td>
</tr>
<tr>
<td>Bev + TMZ + RT</td>
<td>III</td>
<td>New GBM</td>
<td>NCI</td>
<td>RTOG</td>
</tr>
<tr>
<td>Bev + TMZ + RT</td>
<td>III</td>
<td>New GBM</td>
<td>Genentech</td>
<td>Multiple (Europe)</td>
</tr>
<tr>
<td>Bev + TMZ + erlotinib</td>
<td>II</td>
<td>New GBM</td>
<td>NCI</td>
<td>UCSF</td>
</tr>
<tr>
<td>Bev + TMZ + RT, followed by Bev + TMZ + CPT-11</td>
<td>II</td>
<td>New GBM</td>
<td>Genentech, S-P</td>
<td>Duke</td>
</tr>
</tbody>
</table>

**Note:** New GBM; recurrent MG indicates that the study enrolled patients with recurrent GBM as well as those with newly diagnosed GBM.
## VEGFR inhibitors: Selected trials...

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Diagnosis</th>
<th>Sponsor</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cediranib and CCNU</td>
<td>I</td>
<td>Recurrent GBM</td>
<td>AZ</td>
<td>MGH</td>
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<tr>
<td>Cediranib +/- CCNU</td>
<td>III</td>
<td>Recurrent GBM</td>
<td>AZ</td>
<td>Multiple</td>
</tr>
<tr>
<td>Cediranib, TMZ + RT</td>
<td>I/II</td>
<td>New GBM</td>
<td>NCI</td>
<td>MGH, DFCI</td>
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<tr>
<td>CT-322 + CPT-11</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>Adnexus</td>
<td>Multiple</td>
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<tr>
<td>Pazopanib</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>NCI</td>
<td>NABTC</td>
</tr>
<tr>
<td>Pazopanib and lapatinib</td>
<td>I/II</td>
<td>Recurrent MG</td>
<td>GSK</td>
<td>Multiple</td>
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<tr>
<td>Sorafenib and Bev</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>NCI</td>
<td>NCCTG</td>
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<tr>
<td>Sorafenib and erlotinib</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>NCI</td>
<td>NABTT</td>
</tr>
<tr>
<td>Sorafenib and erlotinib, tipifarnib, or</td>
<td>I/II</td>
<td>Recurrent GBM</td>
<td>NCI</td>
<td>NABTC</td>
</tr>
<tr>
<td>temsirolimus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib and temsirolimus</td>
<td>I/II</td>
<td>Recurrent GBM</td>
<td>NCI</td>
<td>NCCTG</td>
</tr>
<tr>
<td>Sorafenib and TMZ</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>Bayer, S-P</td>
<td>Duke</td>
</tr>
<tr>
<td>Sorafenib and TMZ</td>
<td>II</td>
<td>New GBM</td>
<td>Bayer</td>
<td>SCRI</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>II</td>
<td>Recurrent MG</td>
<td>NCI</td>
<td>Multiple</td>
</tr>
<tr>
<td>Sunitinib and CPT-11</td>
<td>I</td>
<td>Recurrent MG</td>
<td>Pfizer</td>
<td>Duke</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>I/II</td>
<td>Recurrent MG</td>
<td>NCI</td>
<td>NCI</td>
</tr>
<tr>
<td>Vandetanib, imatinib, and hydroxyurea</td>
<td>I</td>
<td>Recurrent MG</td>
<td>Novartis,</td>
<td>Duke</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>AZ</td>
<td></td>
</tr>
<tr>
<td>Vandetanib, TMZ+RT</td>
<td>I/II</td>
<td>New GBM</td>
<td>AZ</td>
<td>Multiple</td>
</tr>
<tr>
<td>Vatalanib, TMZ+RT</td>
<td>I</td>
<td>New GBM</td>
<td>Novartis</td>
<td>MGH, DFCI</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DFCI, UCSF, MDACC</td>
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<tr>
<td>XL184</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>Exelixis</td>
<td>MDACC</td>
</tr>
</tbody>
</table>
The Older Paradigm

Bevacizumab vs. Bevacizumab/CPT11

Now

Bevacizumab/Carboplatin
Bevacizumab/Etoposide (VP16)
Bevacizumab/CCNU
Bevacizumab/Daily Temozolomide
Bevacizumab/(5/28 Temozolomide)

So how do we choose which drug? Which drug is the best?

Usually we base it on side effects and on additional factors such as MGMT Status and Blood counts etc.
Responses may be transient.

Radiographic response doesn’t necessarily translate into survival benefit.

A significant proportion of patients don’t respond at all.

**Alternative means of angiogenesis:** (AKA Resistance)

- May develop different forms of VEGF
- upregulation of parallel pro-angiogenic pathways involving FGF, PDGF, angiopoietin
  - increased invasiveness with co-option of native vasculature
Diffuse non-enhancing recurrence...


T1 post-gado

FLAIR

Pre-bevacizumab

4 weeks post-bevacizumab
What about Bevacizumab and Brain metastasis?

Summary: low cerebral hemorrhage rates in all three datasets

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Patients with CNS metastases</th>
<th>Rate of cerebral hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bevacizumab (%)</td>
</tr>
<tr>
<td>A</td>
<td>Bev: n=91, Non-bev: n=96</td>
<td>3.29</td>
</tr>
<tr>
<td>B</td>
<td>n=321</td>
<td>0.93</td>
</tr>
<tr>
<td>C</td>
<td>n=131</td>
<td>0.80</td>
</tr>
</tbody>
</table>

- Reported rates of cerebral hemorrhage from solid tumors metastasized to CNS: 3.5% – 29%\(^1\-^7\)

Cilengitide – Angiogenesis-Inhibitor

Cilengitide (EMD 121974)

- Inhibitor of Integrins \( \alpha v \beta 3 \)
- \( \alpha v \beta 5 \)

- Angiogenesis inhibition
- Direct Anti-tumor activity [?]

CSMC EMD Newly Diagnosed Glioblastoma with Radiation and Temozolomide

cyclo-(Arg-Gly-Asp-DPhe-NMeVal)
Cediranib (Recentin AZD2171)

- A Phase III, Randomised, Parallel Group, Multi-Centre Study in Recurrent Glioblastoma Patients to Compare the Efficacy of Cediranib [RECENTIN™, AZD2171] Monotherapy and the Combination of Cediranib with Lomustine(CCNU)
- Tyrosine Kinase Inhibitor
- Targets all 3 VEGF Receptors
Another piece of the puzzle ....

The PI3K-Akt Signaling Pathway

EGFR Overexpression

- Due to gene amplification
- EGFR amp is present in ~ 50% tumors
- EGFR mutations restricted to tumors with gene amplification
- Most mutations are deletions
  - EGFRvII, EGFRvIII, EGFRvV
  - Lung ca signature mutations not found
- Same mutations present in breast, ovary, lung and prostate Ca.
27% (7/26) had a radiographic response
OS (21.7 vs 5.8 mo, p=0.01) and median time to progression longer in responders (9.7 vs 1.7 mo)

Co-expression of EGFRviii and PTEN predicted response.
However, 5/19 (26%) non-responders had intact PTEN
- 3 amp EGFR and 1-2 EGFRvIII

Mellinghoff et al NEJM 2005
Success in molecular medicine
Oligodendrogliomas/Oligoastrocytomas

• 1p 19q deletion
  – Present in 60 to 90% of oligodendrogliomas
  – Prolonged survival in all grades with treatment with chemotherapy or radiation
  – Highly associated with morphology
    • 84% oligodendroglioma, 15% mixed oligoastrocytoma

• Caveat:
  – Reports of patients without the deletion but with prolonged survival are noted
    • Are usually young patients with low-grade tumors
Summary

1. We are using molecular medicine to predict who will benefit from chemotherapy and personalized medicine is a reality i.e. EGFR, MGMT, 1P19Q, VEGF

2. New Chemotherapies are emerging for the treatment of cancer and older drugs are finding new uses

3. A combined approach using multiple modalities is necessary to defeat brain tumors
Thank You!

- Patient’s and Their Families
- Dr. Keith Black
- Research and Support Staff