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)
INTRODUCTION

A chemotherapeutic agent is a substance that can target and selectively kill transformed cells.

Goals of Therapy

• Resectable Disease (image complete)
  – Prevent relapse
• Unresectable Disease (post biopsy)
  – Prevent Growth
  – Can lead to Surgery?
Principles of Cancer Treatment

Local Therapy
- Surgery
- Radiation therapy

Systemic Therapy
- Chemotherapy
- Hormonotherapy
- Immunotherapy
- Targeted therapy

What is Standard of Care?

- Standard of Care
  - Published/approved standard
    - Peer reviewed literature
    - National meetings, cooperative groups, research groups
  - Community standard of care
    - Rural vs. Urban community
    - Access to care
  - NSI’s standard of care
    - Clinical trials
    - Research on the cusp...
Treatment

• Post surgery (resectable disease)
  - Standard of care: XRT/Temodar
  - Research Protocols: Vaccine Trials
  - Novel Therapeutics

• Unresectable disease
  - NO real standard of care
  - XRT/Chemo/Vaccine
  - Novel Therapeutics

• Relapsed Disease/Recurrence
  - More XRT/stereotactic
  - Chemo
  - Novel Therapeutics

Chemotherapy I

• Chemical Compounds designed to damage your DNA
  - Hope to damage cancer DNA more

• Stops cell growth and division

• Intravenous forms

• Oral agents (Temodar, CCNU, others)

• Side effects
• Generalized Schema of Chemotherapy

Drugs which penetrate the BBB
- Carboplatin
- BCNU/CCNU
- Etoposide (VP16)
- Temozolomide
- Cytarabine
- Tamoxifen
- Procarbazine
- Vincristine
- Methotrexate

Small Molecules
- Cediranib (Pan VEGF)
- Erlotinib

Blood Brain Barrier
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Chemotherapy II

• Limited choices
  - Relapsed and unresectable settings
    • Temodar
    • CCNU/Lomustine
    • BCNU
    • CPT-11

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
- Bendamusine (CSMC Trial)

Carmustine (BiCNU) 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 GIT 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 (Temodar)

3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-1H-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
  - 75 mg/m2 while on RT, wait 4 weeks then re-start with regimen above
What to expect from TMZ?

- Phase III trial chemoradiation:

  - 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>
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<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>
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<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>
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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 to 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.

How do we target?

- **Monoclonal Antibodies (IV)**
  - Literally bind to the cell surface and block.
  - I.e. Avastin.
- **Small Molecule (oral)**
  - Bind to cell surface and block.
  - I.e. Tarceleva.
- **Tyrosine kinase inhibitors (oral)**
  - Block a pathway in the cell.
  - I.e. Gleevec.
- **Multi-kinase inhibitors (oral)**
  - Block multiple pathways in the cell.
  - I.e. Nexavar/Sorafenib, Sutent/Sunitinib.
- **Immunomodulators (oral)**
  - Unknown mechanism.
  - I.e. Thalomid, revlimid.
Is there a target in Gliomas?

- Glioblastoma Multiforme (GBM)
  - Pathologically show increased blood vessel density
  - Laboratory models and animal models predict enhanced angiogenesis (increased blood vessels) as a mode of growth.
  - Theorized that increased T2 enhancement on MRI is due to neo-vascularization
  - Can we reduce enhancement?
    - Does it matter?

Molecularly targeted therapy for Malignant Glioma

Bevacizumab
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.
Characteristics of Cancer


Antiangiogenic Therapy With Avastin

# Angiogenesis inhibitors: Selected drugs...

## Anti-VEGF ligands
- **Bevacizumab (Avastin)**: VEGF-A
- **Aflibercept (VEGF-Trap)**: VEGF-A/B, PlGF

## Receptor Tyrosine Kinase Inhibitors
- **Cediranib, AZD2171**: VEGFR, PDGFR, c-Kit
- **Dasatinib (Sprycel)**: PDGFR, Src, Bcr-Abl
- **Pazopanib, GW786034**: VEGFR, c-Kit
- **Sorafenib (Nexavar)**: VEGFR, PDGFR, c-Kit, Raf
- **Sunitinib (Sutent)**: VEGFR, PDGFR, c-Kit, FLT-3
- **Vandetanib (Zactima)**: VEGFR, IGF, RET
- **Yatalanib, PTK787/ZK222584**: VEGFR, PDGFR, c-Kit
- **Tandutinib, MLN 518**: VEGFR, c-Met

## Others
- **Cilengitide, EMD121974**: αvβ3 and αvβ5 integrins
- **Enzastaurin**: PKC-β and Akt
- **Metronomic chemotherapy**: Tumor endothelium
- **Thalidomide, lenalidomide**: 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
• Better than expected results – Will present data to FDA for approval

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<thead>
<tr>
<th></th>
<th>Avastin</th>
<th>Avastin/CPT11</th>
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<tr>
<td>6 Month PFS</td>
<td>36 %</td>
<td>51 %</td>
</tr>
<tr>
<td>Tumor Response Rate</td>
<td>21 %   (18/85)</td>
<td>34% (28/82)</td>
</tr>
<tr>
<td>MST</td>
<td>8.2 Month</td>
<td>8.7 Months</td>
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Pre & Post Avastin: An Example

PRE

POST

Ktrans  fBV  rCBV

Ktrans  fBV  rCBV
The Older Paradigm

Bevacizumab vs. Bevacizumab/CPT11

Now………………………………

Bevacizumab/Carboplatin
Bevacizumab/Etoposide (VP16)
Bevacizumab/CCNU
Bevacizumab/5-fluorouracil
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....

Cautious optimism...

- 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
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

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
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
    • 81% 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
2. New Chemotherapies are emerging for the treatment of cancer and older drugs are finding new uses
3. New methods are being used to bypass the blood brain barrier
4. A combined approach using multiple modalities is necessary to defeat brain tumors
Thank you