

## Clinical Research: Promise of New Drug Treatments

Asha Das, MD

Presented at:  
*Outsmarting Brain Tumors*

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## Brain Tumors

- Metastatic brain tumors
  - From systemic tumors
    - Lung, breast, gastrointestinal and gynecologic cancers
- Primary brain tumors
  - Variety of histologic types

## WHO Classification

- Neuroepithelial Tumors
  - Astrocytic tumors
  - Astrocytoma (II)
  - Anaplastic astrocytoma (III)
  - Glioblastoma multiforme (IV)
  - Pilocytic astrocytoma (I)
  - Subependymal giant cell astrocytoma
  - Pleomorphic xanthoastrocytoma
  - Oligodendroglial tumors
  - Oligodendroglioma (II)
  - Anaplastic oligodendroglioma (III)
  - Ependymal cell tumors
  - Ependymoma (II)
  - Anaplastic ependymoma (III)
  - Mixed gliomas
  - Mixed oligoastrocytoma (II)
  - Neuroepithelial tumors of uncertain origin
- Tumors of the choroid plexus
- Neuronal and mixed neuronal-glia tumors
- Pineal parenchyma tumors
- Tumors with neuroblastic or glioblastic elements
- Tumors of the sellar region
- Hematopoietic tumors
- Germ cell tumors
- Tumors of the meninges
- Non-meningothelial tumors of the meninges
- Primary melanocytic Lesions
- Hemopoietic neoplasms
- Tumors of uncertain histogenesis
- Tumors of cranial and spinal nerves
- Local extensions from regional tumors
- Metastatic tumors
- Unclassified tumors
- Cysts and tumor-like lesions

## Malignant Brain Tumors

- Surgery
- Radiation
- Chemotherapy or drug therapy
  - Specific tumor types known to be responsive to chemotherapy
  - Children in an effort to delay radiation therapy
  - Recurrent tumors

## Chemotherapy

- What is it and why is it used
  - Chemotherapy uses special drugs to kill tumor cells
  - Primary or first therapy
  - or
  - Adjuvant or additional therapy

## How Does Chemotherapy Work?

- Chemotherapy drugs act on DNA, which is the genetic material found within each cell
- These drugs affect the ability of tumor cells to duplicate their DNA and reproduce

## Side Effects of Chemotherapy

- Affects growing or dividing cells
  - Tumor cells
  - Normal cells
    - Skin
    - Hair
    - Gastrointestinal tract

## Side Effects of Chemotherapy

- Vary from person to person
- Occur during, immediately after, or as delayed reactions
- If the side effects cause discomfort, the dosage may be changed during the course of treatment

## Side Effects of Chemotherapy

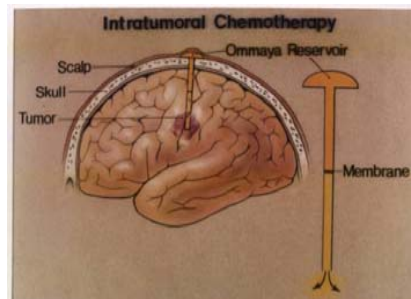
- Bone marrow
  - Red blood cells → anemia
    - Pale, tire easily, or shortness of breath
    - Correct with blood transfusions
  - Platelets → bleeding
    - Correct with platelet transfusions
  - White blood cells → infection
    - Correct with neupogen

## How Is Chemotherapy Administered?

- Oral (po) = tablets
- Intravenous (iv) = into a vein
- Intra-arterial (ia) = into an artery
- Intra-tumoral = into the tumor
- Intrathecal (it) = into the spinal fluid space

## Intrathecal Chemotherapy

- Methotrexate
- Cytosine arabinoside
- Thiotepa
- Trials are underway to study the safety and efficacy of rituximab and topotecan



## Standard Chemotherapy Drug Regimens

## Administration

- Chemotherapy is usually given in cycles
- These cycles are repeated over a specific period of time
- The cycle schedule is designed to allow sufficient time for affected normal cells to recover between treatments

## Standard Chemotherapy Regimens

- Nitrosoureas
  - BCNU (iv)
  - CCNU (po)
- Procarbazine (po)
- Carboplatin (iv)
- Vincristine (iv)

## Temozolomide (Temodar, TMZ)

- Second-generation alkylating agent
- 100% bioavailability
- Rapid, complete absorption:  $T_{max} = 1.1-2.5h$
- Crosses blood-brain barrier
  - Mean CSF/plasma ratio at equilibrium: 40%
- Predictable pharmacokinetic profile
- Cytochrome P450 enzymes not required in metabolism
- No accumulation after repeat dosing

## Newly Diagnosed GBM

- Patient eligibility age 18-70 with newly diagnosed GBM
  - 75 mg/m<sup>2</sup> qd x 6 weeks with concurrent RT 200 cGy x 30 fractions for a total of 60 Gy then Temodar 150-200 mg/m<sup>2</sup> days 1-5 q 28 for 6 cycles
- 573 patients from 85 centers were randomized
- Grade 3/4 hematologic toxicity
  - 7% of patients with concomitant TMZ/RT
  - 16% of adjuvant TMZ

## Newly Diagnosed GBM

	RT (n=286)	RT/TMZ (n=287)	p value
Median survival (95% c.i.)	12 mo (11.2-13.2)	15 mo (13.6-16.8)	p<.0001
2 year survival (95% c.i.)	8% (4-12%)	26% (20-32%)	p<.0001
Median PFS (95% c.i.)	5.0 mo (4.2-5.5)	7.2 mo (5.8-8.3)	p<.0001

## Combinations of Chemotherapy

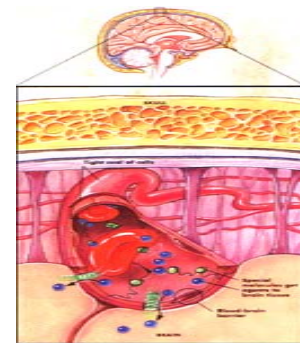
- Temozolomide in combination with
  - CCNU
  - CPT-11
  - VP 16 (Etoposide)
  - Accutane (Isotretinoin)
  - Thalidomide
  - Celebrex
  - OSI 774 (Tarceva)
  - PTK 787 / ZK 222584

## Factors Affecting Levels of Therapeutic Drugs at the Tumor Site

- Concentration of the drug in the bloodstream
- Rate of blood flow to the tumor
- Amount of drug that crosses the blood brain barrier
- Diffusion of drug across the brain parenchyma

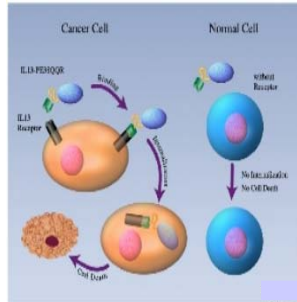
## Blood-Brain Barrier

- The blood brain barrier protects the brain by blocking some drugs from passing through
- Drug delivery to the brain is difficult and incomplete



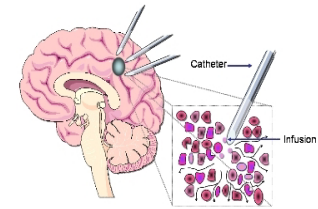
## IL13-PE38QQR

- IL13-PE38QQR is a protein that contains the cytokine IL13
- The protein attaches to tumor cells that have the IL13 receptor and allows the study drug to enter and kill the tumor cells
- Normal brain cells do not have the IL13 receptor and the study drug does not bind to them



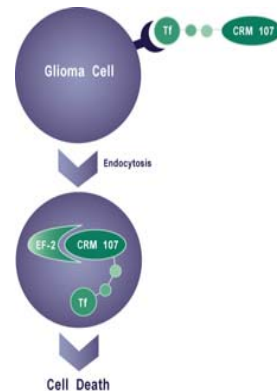
## Convection-enhanced Delivery of IL13-PE38QQR

- Catheters placed in 2-4 areas of tumor
- The drug is continually infused through the catheters
  - A pump is used to slowly push the drug solution
- This treatment is called convection-enhanced delivery or CED
  - Circumvents the blood-brain barrier
  - High local tumor and peritumoral concentrations
  - Minimizes systemic exposure
  - 80% of glioblastomas recur within 2 cm of the primary tumor site



## Transferrin Receptor

- Expressed on all rapidly dividing cells including many different tumor types
- Minimal expression in nondividing tissues (brain)
- Selective delivery of diphtheria toxin (CRM 107) to cancer cells
- Normal cells are spared
- Limited side-effects



## Transferrin Receptor

- Transferrin-CRM107 (TransMID™):  
140,000 MW protein
- Poor penetration of the blood-brain barrier
- Convection-enhanced drug delivery

## Emerging Therapies

- Brain tumors are a diverse group of malignancies that remain refractory to conventional treatment approaches targeted at the molecular changes in these tumors
- Molecular neuro-oncology has now begun to clarify and identify pathways that might be amenable to targeted therapy
- Although these molecular therapies are in the early stages of clinical development and evaluation they represent a shift in treatment strategy

## Newer Drug Therapies

- Attach to receptors on the surface of tumor cells
- Block proteins within the tumor cell
- Affect the blood supply to tumors

## Drugs

- Induce damage to DNA
  - BCNU
  - Procarbazine, CCNU, Vincristine
  - Temozolomide
- Inhibit mitoses
  - Taxol
  - BMS-247550
  - CI 980
- Inhibits tumor growth pathways [(PI3K)/Akt pathway ]
  - Wortmannin
  - LY-294002
- Inhibit proliferation
  - Atrasentan (ABT-627)
  - Irofulven (MG 1140)
- Inhibit Topoisomerase I
  - Irinotecan (CPT 11)
  - Topotecan
  - Pyrazoloacridine
  - Karenitecin (BNP 1350)
- Inhibit sonic hedgehog/ PTCH pathway (medulloblastoma)
  - Cyclopamine

## Angiogenesis

- Formation of new blood vessels is critical for the development and progression of brain tumors.
- Targeted approaches to inhibit angiogenesis include
  - Vascular endothelial growth factor receptor (VEGFR) inhibitors

## Anti-angiogenic Drugs

- Anti-angiogenic drugs inhibit new blood vessel formation
  - Thalidomide
  - Avastin (rhuMAb-VEGF)
  - CC 5013 (Revimid™)
  - PTK 787/ZK 222584
  - EMD-121974
  - ZD6474
  - LY317615 (Enzastaurin)
  - Cannabinoids  
(inhibit genes needed for production of VEGF)

## Differentiating Agents

- Tumor cells divide and infiltrate because they lack normal growth mechanisms
- Differentiating agents make a cancer cell behave more like a normal healthy cells
  - Retinoids
    - cis-Retinoic acid (Accutane)
    - Fenretinide (4HPR)
  - Phenylbutyrate
  - Phenylacetate

## Cell Signal Transduction

- Enzymes within the cell control
  - Growth
  - Function
  - Resistance to standard treatment
- Drugs that block or alter these enzymes inhibit tumor cell growth and resistance to treatment

## Cell Signal Transduction Modulators

Enzyme	Drug
O6-alkylguanine-DNA alkyltransferase	O6 benzylguanine
Farnesyl transferase inhibitor	R 115777 (Zarnestra)
Inhibition of protein kinase C	Tamoxifen Bryostatin
Protein kinase C-alpha	LY900003 (ISIS 3521)
Inhibition of enzyme mTOR	Rapamycin (tablets) CCI-779 (iv) RAD001

## Growth Factor Inhibitors

- Normal cell growth is controlled by growth factors
  - Vascular endothelial growth factor
  - Platelet derived growth factor
  - Tyrosine kinase
  - Epidermal growth factor
- Blocking the production or action of these growth factors halts tumor growth



## Growth Factor Inhibitors

- ZD 1839 (Iressa)
- OSI 774 (Tarceva)
- AEE788 (EGFR)
- STI 571 (Gleevec)
- SU 5416
- Transtuxumab (Herceptin)
- SB431542 (TGF-beta)



## Future Trends

- Certain proteins expressed in higher than expected concentrations in blood vessels within the tumor
  - Determine the function of these proteins
  - Find methods to augment or reduce their expression that help eradicate tumor
- Markers for chemosensitive tumors
- Determine optimal combinations of chemotherapy



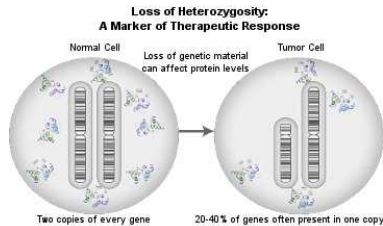
## Markers for Chemosensitive Tumors

- Anaplastic Oligodendroglioma
  - Genetic losses (1p and 19q) are near genes for DNA repair enzymes
  - Due to lack of DNA repair mechanisms, these tumors are susceptible to chemotherapy



## Loss of Heterozygosity (LOH)

LOH indicates loss of a part of the chromosome



## Anaplastic Oligodendroglioma

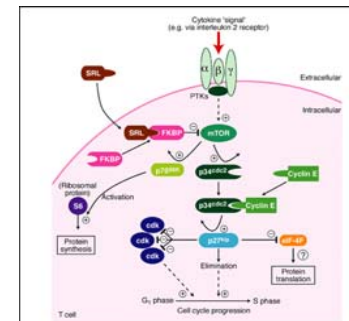
	Response to chemotherapy	5-year survival
LOH 1p	100%	95%
LOH 1p+19q	100%	95%
No LOH	31%	25%

## Gefitinib (Iressa)

- Growth factors of the epidermal growth factor (EGF) family have been implicated in cancer development and progression
- In GBM, the epidermal growth factor receptor (EGFR) contributes to malignant progression
- Gefitinib inhibits EGFR
  - Inhibits cell division and causes cell death
- Ability to cross the blood-tumor barrier
  - Responses of intracranial metastases secondary to non-small cell lung cancer

## Mammalian Target of Rapamycin (mTOR)

- mTOR plays a significant role in promoting tumor growth via multiple pathways
- Rapamycin binds intracellularly to FKBP12
- The resultant complex inhibits mTOR activity

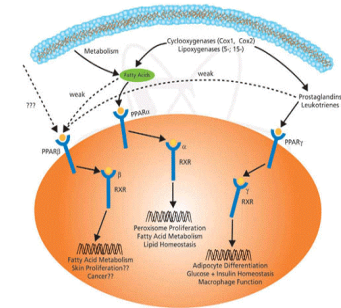


## EGFR and mTOR Inhibitors

- The potential synergistic effect of a combination of EGFR and mTOR inhibitors
  - In cervical squamous cell carcinomas a combination of mTOR and EGFR inhibition resulted in significant tumor growth delay
  - Combination treatment with mTOR and EGFR inhibitors have resulted in a synergistic effect that suppressed growth of glioma cell lines

## Nuclear Hormone Receptor (NHR) Family PPAR $\gamma$

- Expressed in adipose tissue
- Expressed prominently in a variety of cancer cells possesses tumor suppressive activity
- Pioglitazone is a highly selective agonist for PPAR $\gamma$ 
  - FDA approved for type 2 diabetes



## Isotretinoin (Accutane)

- Another NHR, the retinoic acid receptor (RAR), is expressed in glioblastoma cells.
- The ligand for RAR, all-trans retinoic acid (ATRA), inhibits growth of glioblastoma cell in vitro.

## PPAR $\gamma$ (PGZ) and RAR ligand (IST)

- In *in vitro* and *in vivo* studies, the combination of ligands for PPAR $\gamma$  (PGZ) and RAR ligand (ATRA)
  - Inhibited growth of human breast cancer cells synergistically and induced cancer cell apoptosis
  - Induce apoptosis and inhibit the proliferation of glioblastoma

## Summary

- Standard chemotherapy
- Novel drugs and drug combinations



THANK YOU

This presentation may be downloaded from  
[www.cedars-sinai.edu/braintumor](http://www.cedars-sinai.edu/braintumor)

