

Therapy for Brain Tumours June 2006

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When a Brain Cancer is diagnosed

- The surgeon sends off the Tissue to the pathologist
- The pathologist studies the cancer cells with a Light Microscope

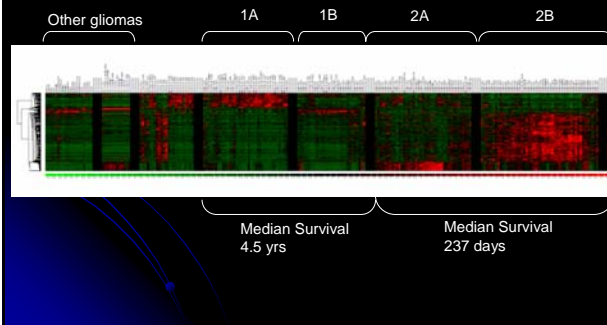
- They make the diagnosis by
 - The way the cell looks
 - The effects the malignant cells have had on the environment they are growing in
- They then diagnose
 - Astrocytoma- grade 2
 - grade 3
 - grade 4- glioblastoma multiforme (GBM)

Or

- Oligodendroglioma
- Anaplastic Oligodendroglioma

- Although their classification is based on what the cells look like it doesn't mean all cells that look the same behave the same
- The way tumours behave is determined by their genetic make-up
- This means some tumours will be sensitive to certain therapies, whereas others may not

Genetic Profile of Gliomas



Scientists are looking for better ways of classifying these tumours at a molecular level

- We already know for Oligodendrogliomas- that certain missing genes predict a sensitivity to chemotherapy
 - The 1p 19q test
- This kind of molecular identification will become very important as more targeted drugs are developed
- There will be no point giving someone a targeted treatment if the tumour doesn't have the target

Radiotherapy

- Although these tumours may look localized on MRI scans, they extend in a "Spider Web" pattern way beyond the area of enhancement seen on MRI and there is no way of the surgeon knowing exactly where they are
- Unlike Breast Cancer, where the surgeon can remove the "lump", then a "margin of normal tissue- 2cm around the lump, in brain cancer surgery this is not possible, so there will always be malignant cells left behind

- We use radiation to "mop" up those outlying cells
- The area that receives radiation, and the dose of radiation delivered, is determined by careful computer planning, taking into account the size and shape of the original tumour

Chemotherapy

- Another way to “mop” up these rogue cells is with chemotherapy

How does Chemotherapy work?

- There are about 100 different chemotherapy drugs
- They can be delivered as
 - Tablets or capsules
 - Intravenous injections or infusions
 - Local delivery in “wafers” or via catheters in the surgical cavity

Once they have reached the blood stream

- They may go through the liver and be activated or degraded
- They circulate through the whole body eventually reaching the site of the cancer
- They are like a
 - POISONTo the cells they come in contact with

- Normal cells can be damaged by the chemotherapy, but because their “Computer” is still functioning normally, they can repair the damage which chemotherapy causes and keep on functioning
- Cancer cells, on the other hand have “Malfunctioning Computers” and sustain lethal damage from the drugs
- Chemotherapy is usually delivered at TIME INTERVALS, that allow the normal cells to recover, but hit the cancer cells again while they are still down

Cancers that start in different organs are susceptible to different drugs

- When a new drug is discovered it goes through a process of testing
 - Phase 1- to find out the optimum safe dose to use in humans
 - Phase 2-about 50 people with the same cancer are given the drug-and the number of people who respond are documented
 - Phase 3-when a new treatment looks promising it is compared to what we already have as standard to see if it can improve things-up to 500 people

Drugs with activity in Gliomas

- Nitrosureas- BCNU CCNU
- Procarbazine
- Carboplatin-Cisplatin-Cisplatin
- Etoposide=Vepesid
- Camptosar=Irinotecan=CPT 11
- Temozolomide

Nitrosureas-BCNU CCNU

- Old drugs
- Traditionally used in combination with Vincristine and Procarbazine

They are usually given every 6-8 weeks

Other agents-

- The problem with a lot of chemotherapy trials of newer drugs is that they did not take into account the impact anti-convulsant (drugs used to stop seizures) had on other drug metabolism
- Phenytoin(Dilantin) and Carbamazepime (Tegretol) can switch on the liver to make it detoxify some other drugs at 5 times the normal rate

- Many trials were done using the same doses of chemo that would be used in someone not on anticonvulsants meaning the brain tumours were only exposed to tiny doses-nothing happened and the drug was thought to be "Inactive"
- We now know if we want to test a new drug against brain tumours we must 1st find out what the best dose is to give someone on anticonvulsant drugs

Etoposide (Vepesid) and Camptopar

- These are 2 older chemo drugs used to treat other cancers
- They do seem to kill some brain tumours but they are very difficult to give as they are greatly affected by anticonvulsants and we don't have the complex biochemistry facilities to accurately monitor them

Temozolomide

- This drug was discovered about 10 years ago in the UK
- It comes in a capsule, and once swallowed enters the liver where it is activated to produce anti-tumour effects
- It is not affected by anticonvulsant medications
- It has been used for about 10 years- initially in trials and then commercially for patients whose brain tumours that had recurred after surgery and radiotherapy

What's new?

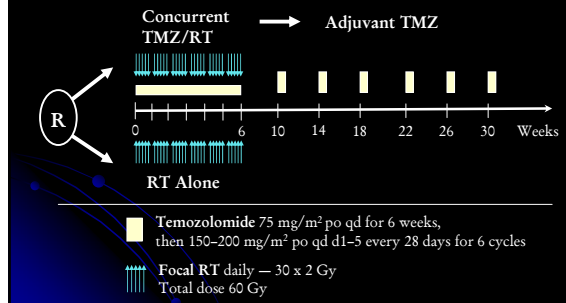
- A trial, started about 5 years ago, tested if we gave everyone with a newly diagnosed GBM low dose Temodal during radiotherapy and then for 6 months after completion of radiotherapy, whether it could improve outcome for GBMs
- This trial was a phase 3- involved 573 patients, and compared Temodal-radiotherapy to radiotherapy alone
- It was published in May 2005 and led to the Australian government agreeing to pay for Temodal for all patients with GBM from 1st June 2005

Baseline Patient Characteristics

	RT Alone n=286	TMZ/RT n=287
Median age	57 (23-71)	56 (19-70)
M/F (%)	61/39	64/36
PS 0-1 vs 2 (%)	87/12	86/13
Baseline corticosteroids (%)		
Yes	75	67
No	24	33

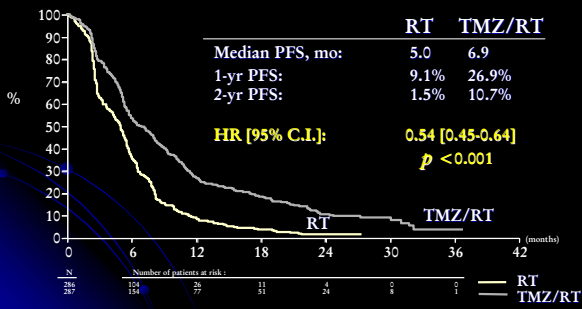
Stupp R et al. NEJM 2005;352:987-96.

Treatment Schema



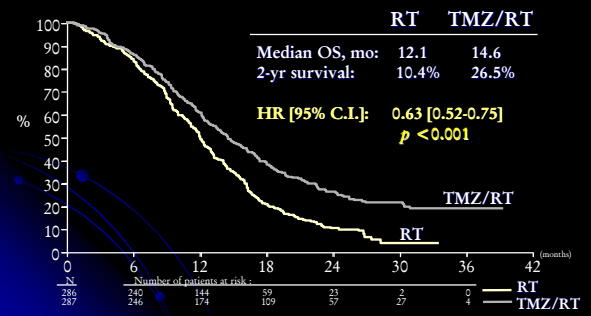
Stupp R et al. NEJM 2005;352:987-96.

Progression Free Survival



Stupp R et al. NEJM 2005;352:987-96.

Overall Survival



Stupp R et al. NEJM 2005;352:987-96.

Combination Temodal- DXRT

- This has become “ Standard of Care” for anyone newly diagnosed with a GBM
 - ie: everyone is considered for this treatment
- There may be cases however when we do NOT recommend having the Chemo-Radiation together as it can have side-effects

This trial was only done on patients with GBMs

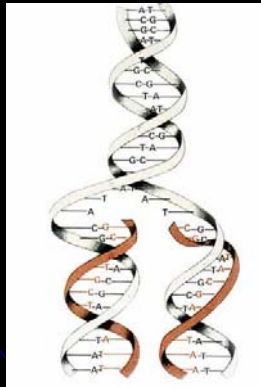
- We cannot just assume that something that is good for GBMs is good for good for lower grade tumours
- Even with this treatment only 26% of GBM patients were alive at 2 years
- Patients with grade 2 & 3 astrocytomas and Oligodendrogliomas have a much longer life expectancy- and therefore if this treatment has any long term DOWNSIDES that don't emerge for 3 or 4 years- they will be affected

What is new????

To find a treatment for brain tumours we must

- Understand exactly what the tumour cells are made up of and how they differ from normal brain
- Every cell in the body is controlled by a COMPUTER- the genes it is composed of





The Computer- the DNA – which make up the Genes control how a cell behaves

- How often it divides
- How it functions
- Whether it can travel
- Whether it is susceptible to certain drugs

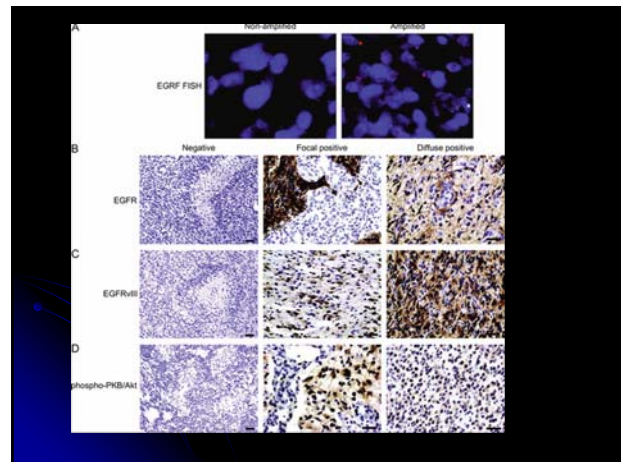
Cells are constantly interacting

- With each other
- With other cells in their environment
- Every cell in our body contains the same set of genes which are unique to an individual
 - eye- skin- brain
 - That is how forensic scientists can identify individuals at crime scenes

The environment in which a cell is living determines what genes are switched on and off and therefore how the cell behaves

How do cells communicate

- The surface of each cell is covered with "Receptors" (letter boxes), which can be triggered by circulating molecules
- These molecules can come from
 - Other nearby cells
 - Through the circulation
- Once "triggered" on the surface, they set off a cascade of events throughout the cancer cell which can cause it to divide
- By blocking these the receptors the cell may be starved of a vital element and die



The surface of a cell contains "RECEPTORS"

- When a surface receptor is activated- it carries a signal into the nucleus where the genes are contacted and switched on and off via rapid biochemical pathways
- The genes respond to these signals and may send other signals out into the environment or shut down certain functions within the cells

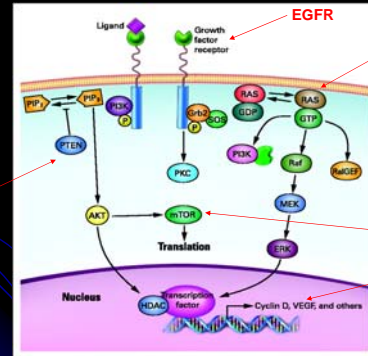
When the genes get damaged and a cell becomes a CANCER cell

- They may have
 - Abnormal receptors-
 - There are too many of them
 - They respond to the wrong signals
 - The genes that control how often cells divide and when they die are damaged
 - The "Cell Cycle" is out of control
 - They just keep on dividing
 - They forget to die

By studying these “Molecular” pathways

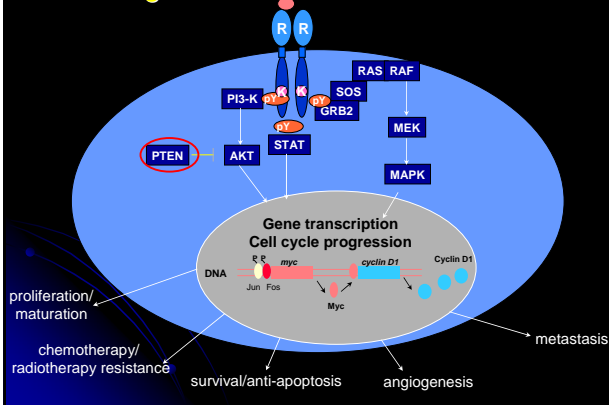
- We can come up with pathways that are unique to Cancer cells-
 - And then design SMART drugs-
 - TARGETED THERAPIES
 - that will only cause harm to cancer cells and not the normal cells

Aberrantly activated signaling pathways in malignant glioma



Reardon, D. A. et al. J Clin Oncol; 24:1253-1265 2006

EGFR signal transduction in tumor cells



Small Molecules

- Drugs that can target cell surface receptors
 - EGF- inhibitors
 - Iressa Tarceva
 - PDGF inhibitor
 - Glivec
 - Multiple target inhibitors
 - Enzastaurin
 - TOR inhibitors

The disappointment

- Even if the cells have EGF- receptors, it doesn't mean that the EGF blocking drugs will necessarily help
- The "molecular" story is turning out to be a lot more complex

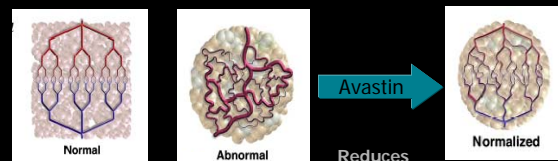
Drugs that can "stabilize the environment where the cancer cells are thriving"

- Anti-angiogenic agents-AVASTIN

Angiogenesis is essential for sustained tumour growth

Modified from Folkman J. N Engl J Med 1971;285:1182-6

Anti-angiogenic therapy: effects on human tumour vasculature



Reduces
interstitial fluid pressure
vessel density

Increases
drug delivery

Adapted from Jain RK. Nat Med 2001;7:987-9
Willett CG, et al. Nat Med 2004;10:145-7
Tong R, et al. Cancer Res 2004;64:3731-6

Where does that leave patients right now?

- Right now, there are a number of new drugs that MAY be useful for the treatments of Gliomas
- Until properly tested, they will NOT become generally available
- Of the 1000 drugs that start out in the lab, only 1 will make it through to patients
- It costs millions of dollars, from discovery to commercialization

- It also takes many patients to participate in clinical trials, to be “guinea pigs”, to test whether these drugs are
 - Useful
 - Safe
- Most trials now are trying to correlate genetic makeup of tumours with outcome, so in the future we may be able to select the right drug for the right patient

- Unfortunately, all these trials take TIME, but if done correctly will have a big impact on treatment for future patients