

Brain Tumors – TREATMENT

Updated: April 24, 2010

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Treatment planning demands **tissue diagnosis!** see p. Onc1 >>

Final goal of therapy - **CYTOREDUCTION** - decrease of total tumor mass to size that immune system might suppress and eventually kill (for gliomas it is ≈ 0.0001 g, or 1×10^5 cells).

For **NEUROECTODERMAL TUMORS**, *likelihood of cure is small* and *risks to brain are large*; to improve therapeutic ratio, **multimodality treatment** is rule:

- 1) **surgery** – usually only $< 50\%$ of tumor mass can be resected, thus leaving residual tumor burden of $1-5 \times 10^9$ cells;
 - surgery is only form of therapy in which tumor cells are not only *killed* but actually *removed* (body's capacity to remove debris from brain is less than that for other organs - removal of dead tumor tissue is valuable adjunct).
 - if tumor bulk is reduced, quiescent cells enter active growth phase, making them *more susceptible* to radiation / chemotherapy!
- 2) **radiotherapy** might kill two additional logs of cells, reducing tumor to 1×10^7 cells;
- 3) **chemotherapy** must then kill two additional logs to reduce burden to desired 1×10^5 cells.
 - current chemotherapy produces net cell kill of only about 1 log and thus tumor grows despite drug administration.

Present-day multimodality therapy can treat infiltrative brain tumors but can rarely cure them.

Any treatment modality requires **measure of response to treatment** - **contrast-enhanced MRI** (or less desirably, CT):

- a) tumor growth (deterioration)
- b) tumor regression (response).

SYMPTOMATIC TREATMENT

VASOGENIC EDEMA

ICP \uparrow accompanies majority of brain tumors - start **DEXAMETHASONE** in every patient promptly!!!

- small **MENINGIOMAS** or **ACOUSTIC NEUROMAS** usually do not require treatment to reduce ICP.
- **DEXAMETHASONE** is steroid of choice (no mineralocorticoid activity, best CNS penetration).

Dosage - start with oral loading dose of 24 mg \rightarrow 4 mg \times 4/d. (or 8×2).

for children – start 0.5-1 mg/kg \rightarrow 0.25-0.5 mg/kg divided into 4 daily doses.

- well absorbed by mouth - action is almost as rapid as when given IV (can be switched from IV to PO regimen in 1:1 ratio).
- induces **improvement within 48 hours** (usually sooner);
 - if no benefit, - neurologic symptoms are due to damage of brain tissue by tumor (i.e. not to edema);
 - consider CSF diversion procedure because various degree hydrocephalus is frequent.
- *lowest dosage* that maintains patients at maximum level of comfort and function should be sought (decrease dosage until symptoms increase or become apparent \rightarrow increase dosage until they subside).
 - N.B. tumor growth or treatment-induced effects may require dosage \uparrow ; decrease in steroid requirement suggests improvement.
- some form of antiulcer agent is used (e.g. H₂-blocker).

In instances of **extreme intracranial pressure**, speed and action of dexamethasone are not sufficient \rightarrow add **MANNITOL**. see p. S50 >>

- it is unusual for patients to decompensate preoperatively so severely that intubation becomes necessary (nevertheless, this does occur).

N.B. injudicious use of hyposmolar 5% dextrose IV often is sufficient to produce abrupt increase in brain edema and herniation.

SEIZURES

It is conventional (but not clearly effective) to **treat all supratentorial tumors with anticonvulsants** before surgery.

- **posterior fossa tumors** have low probability of convulsive seizures (no need for anticonvulsants); for **subcortical tumors** prophylactic anticonvulsants are also probably unnecessary.
- in general, meta-analysis concluded that no data support use of prophylactic anticonvulsant!

PHENYTOIN is best initial drug (can be continued IV during perioperative period):

- start orally (1000 mg* over 12 hours) or IV (1000 mg over 1 hour) → 300-400 mg/d in one dose or split between breakfast and dinner; *for children - 4-8 mg/kg/d
- periodic blood level checks - keep at [10-20 mg/mL].
- if required, patients may be switched easily to alternative oral drugs later.

PSYCHIATRIC PROBLEMS

- some patients derive tremendous help from each other in organized support groups.
- **depression** is often significant problem → appropriate **pharmacotherapy**.
- **fatigue** is common (esp. during and after radiotherapy) → **stimulants**: **PEMOLINE**, **PROTRIPTYLINE**.

OTHER PROBLEMS

- no restrictions are placed on **activity** (patients' activity relates to overall neurologic status).
- **ventricular drainage** if **hydrocephalus** is present.
- patients with neurologic deficit and immobility are at risk for **deep vein thrombosis & pulmonary emboli** - **anticoagulation** should be considered (recent reports suggest - risk of tumor bleeding with use of anticoagulants is not as high as was once feared, but prophylactic use of anticoagulation is not recommended).
- **hospice groups** (available in many locations) can be exceedingly helpful in managing **final phase of illness**.

SURGICAL TREATMENT

In almost every instance in which brain tumor is diagnosed, *first consideration is its surgical resectability!* (exception - multiple brain metastases)

Surgery should be first therapeutic modality for tumor!

Goal - resection of **maximal amount** of tumor consistent with **functional preservation**

- even potentially curable tumors (such as **MENINGIOMAS** or **ACOUSTIC NEUROMAS**) may reside in positions that make complete resection technically impossible!
- in era of modern neuroanesthesia, it is rare that craniotomy must not be done because of poor general medical status.
- surgery is scheduled on elective, but preferably urgent, basis.

INTRA-AXIAL TUMORS

- usually **not amenable** to RADICAL surgical resection;
 - most gliomas lack microscopic boundaries!; glioma cells may migrate several centimeters along white matter pathways, including corpus callosum, making complete resection impossible.
 - nonglial tumors generally grow by expansion.
- debulking of malignant gliomas has some benefit.
 - N.B. **brain stem tumors** are not amenable to surgical therapy (even biopsy is hazardous!)
- single brain metastasis is indication for surgical resection (depending on systemic medical status).
- avoid **radical*** operations on tumors involving: language areas, sensorimotor regions, basal ganglia, corpus callosum, brain stem.
 - ***partial** removal may be surprisingly effective (if resection is confined to tumor itself, it rarely produces major new neurologic deficits)
- **functional imaging** facilitates surgery by showing that tumor has pushed aside critical brain structures.

EXTRA-AXIAL TUMORS

- **potentially curable** by surgery, but often located in regions that are difficult to reach surgically.

PREOPERATIVELY

- **DEXAMETHASONE** should be administered at least for few days preoperatively.
- preoperative **angiography** is important in some tumor types. see p. Onc1 >>
 - preoperative **embolization** can decrease intraoperative blood loss.

ANESTHESIA

- **anesthesia** with lack of effect on ICP.
 - increasing number of resections in dominant hemisphere are done under local anesthesia for purpose of speech mapping.
- **MANNITOL** (1 g/kg) + **hyperventilation** (P_{CO2} 25-30 mmHg) for definitive ICP reduction in preparation for brain retraction.
- some routinely administer **BROMODEOXYURIDINE** IV (during induction of anesthesia) - tumor labeling on fixed tissue postoperatively.
- about **5-ALA CHEMORNAVIGATION** see below

PROCEDURE

- **prone** position is comfortable for surgeon; **sitting** position - risk of air embolism, less comfortable for operating physician, but field is much clearer because drainage is easier.
- head is held rigidly with **pin fixation** to minimize movement (for infants, use **soft rings** - pins can perforate infant's skull or cause depressed fracture).
- dura is opened only after brain has been softened completely by **mannitol diuresis** and **intraoperative hyperventilation** (sometimes few minutes' wait is necessary - this brief pause can be critical to success!).
- mapping of eloquent cortex by **electrical stimulation of cortex**.
- **intraoperative cranial nerve monitoring** alerts surgeon when nerves are at risk of damage; cranial nerves II-XII can be monitored intraoperatively (e.g. CN7 monitored with EMG, CN8 monitored with BEAR).

- **intraoperative electrocorticography (ECOG)** is useful in tumor-associated epilepsy (esp. in long-standing or severe seizures).

APPROACH

Tumors that reach cortical surface are approached through **craniotomy at that site**.

Subcortical tumors are approached through:

- deep sulci** (vs. gyral crown) avoiding eloquent areas (e.g. approaching lesion obliquely).
 - cortical incision is \approx 3 cm in length.
 - anterior corpus callosum** (causes minimal, if any, deficit).
 - dilated ventricles** (intraventricular neoplasms).
- localization of subcortical tumors:
 - intraoperative ultrasonography
 - frameless MRI-guided interactive surgical system (markers on patient's scalp).

Skull base tumors:

Anterior skull base:

- tumor behind orbit (incl. tumors of gasserian ganglion and cavernous sinus) → **orbitozygomatic approach** (osteotomy through zygoma and orbital roof).
- tumors in sella turcica → **trans-sphenoid approach**.
- tumors of upper one third of clivus, lesions of odontoid process → **transoral** or **transpalatal approach** (may be extended by osteotomy of mandible).
- tumors of paranasal sinuses and upper one third of clivus → **transfacial approach** (to expose mandible for osteotomy, midface can be degloved).

Lateral approaches through temporal bone to middle skull base (e.g. petrosal or presigmoid approach in which petrosal bone is drilled away).

Posterior approaches:

- extreme lateral approach** - exposes lower third of clivus, cerebellopontine angle, and petrous surface temporal bone.
- lesions of cerebellopontine angle → **retromastoid craniotomy**.
- lesions of petrous surface of temporal bone → **suboccipital craniotomy**.

TUMOR REMOVAL

- grasping instruments, sponges, suction. see p. Onc5 >>
 - removal of **firm, adherent, or calcified tumor** is simplified by **Cavitron ultrasonic aspirator (CUSA)** - tip vibrates at 22,000 Hz - ultrasonically disrupts tumor; tip is surrounded by two concentric channels, one dispensing saline to solubilize fragments and another suctioning away that suspension.
 - allows for internal debulking of large tumors and reduces amount of brain retraction needed for tumor removal.
 - in **limited access locations**, **CO₂ laser** can vaporize tumor tissue with hands-off technique (such tumor removal is slow).
- resection proceeds from inside out (so that surrounding normal white matter is disturbed minimally).
- glistening peritumoral white matter is seen easily through microscope as tumor's margin is reached - at this interface resection is stopped.
- if both arterial and venous supplies of structure are to be sacrificed, arterial supply should be interrupted first (to avoid congestion, bleeding, and swelling).

Fluorescence-Guided Resection (s. chemonavigation):

- 1 g of **5-aminolevulinic acid (5-ALA)** is taken PO 2 h before surgery.
- 5-ALA leads to accumulation of fluorescent porphyrins (protoporphyrin IX) in tumor tissue.
- target region is exposed to laser light with 405 nm peak wavelength (with hand-held device):
 - laser light is blue.
 - tumor tissue glows red.
 - surrounding infiltrated tissue glows orange.
- after operation, avoid direct sunlight for 24 hours.

CLOSURE

- **hemostasis** is sometimes difficult but must be perfect.
- if **brain swelling** is worrisome at time of closure (rare situation), ICP catheter is left in subdural space.
- **tumor cysts** can be drained and, when possible, fenestrated into adjacent ventricle to prevent reaccumulation.
- about CSF drainage → see p. Onc18 >>

POSTOPERATIVELY

- ICU for at least 1 night.
- extubation:
 - if surgery entails significant manipulation of brain stem, patient should remain intubated for first postoperative night and be extubated carefully once lower cranial nerve function has been assessed;
 - if brain stem involvement was minimal, patient may be extubated in operating room.
- **keep relative dehydration** - serum **electrolyte levels** and **osmolality** are measured often (also to detect possible onset of inappropriate secretion of ADH or diabetes insipidus).

Continue **DEXAMETHASONE** for at least 5 days (to minimize surgically induced brain edema);

- if adequate surgical decompression is achieved, steroid can be discontinued within first 1-2 weeks.
- indications for steroid maintenance:
 - large volume of tumor remains
 - tumor in brainstem or spinal cord
 - steroid dependence.
- corticosteroids again may be needed during or after radiation therapy.

Continue **anticonvulsants** for at least 1 year.

Antiembotic measures:

- compression boots → early passive exercises and mobilization!!!

POSTOPERATIVE IMAGING

- **contrast MRI within 2 days** - to evaluate resection success (later, prominent enhancement of neovascularized reactive gliosis develops - may interfere with image interpretation); absence of abnormal enhancement on postoperative CT indicates gross total resection.
- for tumors with **propensity for leptomeningeal spread** (**MEDULLOBLASTOMAS**, **EPENDYMOMAS**, **CHOROID PLEXUS CARCINOMAS**, certain **PINEAL GERMINOMAS**), test before further postoperative therapy:
 - CSF cytologic examination** at least 2 weeks after surgery (LP is safe \approx 10-21 days after intracranial decompression);
 - some authors suggest obtaining CSF at time of surgery from cisterna magna for cytologic analysis.

- 2) **spinal MRI** yearly during first 24 months (CSF exam alone is inadequate – may be false-negative in up to 50% cases); routine spinal evaluations beyond this time may not be practical (local recurrences are far more likely).

– if MRI is contraindicated, CT myelography is utilized.

N.B. **baseline** spinal MRI is best done *prior to surgery* (to avoid postoperative artifacts); first **postoperative** spinal MRI - *at least 2 weeks after surgery* (spinal canal enhancement can occur in early postoperative period); if equivocal → repeat after 1-2 weeks (artifacts secondary to surgery regress while drop metastasis remain stable or increase).

ROUTINE SURVEILLANCE (unwarranted in *asymptomatic* patients following *complete resection* of *benign* tumors):

- every 3-6 months during first 2 years;
- every 6-12 months for following 2-3 years
- every 3-5-years (for detection of late events such as radiation-induced meningiomas).

- residual or recurrent contrast enhancement ≥ 2 months after surgery suggests **recurrence**.
- differentiation of **residual tumor** from **scar** (region of linear, rim enhancement) is improved by gadolinium.

COMPLICATIONS

- current operative MORTALITY rates are < 1%.
- operative MORBIDITY depends largely on tumor location (highest – 10-20% – in diencephalic tumors).

REOPERATION

- is effective for **recurrent tumors**.
- directed toward **preservation of quality of life** during survival.
- if there is some modality (chemotherapy or brachytherapy) that patient can receive after reoperation, then resection must be aggressive.
- tissues are compromised by previous therapy - **postoperative infection** rate is high!

RADIOTHERAPY

about PRINCIPLES, COMPLICATIONS (incl. radiation necrosis) → see p. Rx11 >>

After surgery, patients* receive full dose radiotherapy.

*for children < 3 yrs. (age by which myelination is thought to be complete), try to delay radiotherapy or use reduced doses (as compensation use chemotherapy); in **MEDULLOBLASTOMA** radiotherapy is so effective that is used in children despite its adverse consequences!

- radiation therapy is outpatient procedure.
- timing of radiation therapy** - early may be better therapeutically, but brain can be exposed to radiation damage earlier than necessary.
- start **corticosteroids** for at least 48-72 hours before radiotherapy (dose can usually be tapered relatively early, and often discontinued after 1-2 weeks).

External beam radiation therapy is generally given in:

daily fractions of 1.72-2 Gy/d 5 days per week

Target volume varies according to histopathology (also account for patient movement and daily set-up uncertainties):

Target volume	Tumor types
local field with narrow margins of surrounding normal tissue	MENINGIOMAS, PITUITARY ADENOMAS, CRANIOPHARYNGIOMAS, ACOUSTIC NEURILEMMOMAS
local field* with larger margins	ASTROCYTOMAS, OLIGODENDROGLIOMAS
whole brain	LYMPHOMA
entire CNS (craniospinal axis)**	PRIMITIVE NEUROECTODERMAL TUMORS (incl. MEDULLOBLASTOMA), NEUROBLASTOMA, GERM CELL TUMORS, PINEOBLASTOMA, CHOROID PLEXUS CARCINOMA, some EPENDYMOMAS (infratentorial or high-grade)

*studies have failed to demonstrate that irradiating whole brain is superior to more limited fields
 **damages vertebral bone marrow - leaves little reserve for chemotherapy (H: colony-stimulating factors)

Total dose depends on tumor histopathology and on CNS tolerance (depends on age):

- for **MALIGNANT GLIOMAS**, total dose ≈ 60 Gy (over 5-6 week period).
METASTASES are treated with whole-brain radiation in smaller number of fractions (dose 30 Gy).

Total dose and dose-fractionation in children (single daily fractions of 1.8 Gy 5 days per week):

Age	Local fields	Whole brain	Spinal axis
< 3 yrs*	50.4 Gy/28 fx/6 wk	39.6 Gy/22 fx/4.5 wk	30.4 Gy/19 fx/4 wk
≥ 3 yrs	54 Gy/30 fx/6 wk	45 Gy/25 fx/5 wk	36 Gy/20 fx/4 wk

*children < 3 yrs pose significant risk of injury - dose reductions of 20-25% are common (some advice chemotherapy, in attempt to delay radiation).

For **lesions < 4 cm**, **radiosurgery** can be administered (high dose in single session): meningiomas, acoustic or trigeminal neuromas, recurrent pituitary adenomas, solid residuals of craniopharyngiomas, hemangioblastomas, malignant sharply localized tumors, small metastases, selected gliomas (thalamus or brainstem).

Indications for **brachytherapy**:

- selected **recurrent** tumors
- some **well-localized** lesions
- adjuvant** to external-beam radiotherapy if high risk for local treatment failure.

N.B. intralesional **radionecrosis** is frequent (mass effect may necessitate surgical intervention)!

Currently, attention is turning away from **brachytherapy** and toward use of **stereotactic radiotherapy** as technique to increase local tumor doses

Radiocolloidal solutions - may be placed into **cystic cavities**.

PATHOPHYSIOLOGY

- most primary CNS neoplasms**:
 - are **unifocal** - potentially curable with local therapy.
 - infiltrate for considerable distance** into surrounding normal CNS tissue - need to irradiate substantial amount of normal tissue (tolerance of these tissues becomes limiting factor).

- radiosensitivity:
 - Radiosensitive tumors:** PRIMARY CNS LYMPHOMAS, PRIMITIVE NEUROECTODERMAL TUMORS (incl. MEDULLOBLASTOMAS), GERMINOMAS.
 - Radioresistant tumors:** MENINGIOMAS, ACOUSTIC NEUROMAS.

CHEMOTHERAPY

- adjunctive therapy for highly aggressive and infiltrating neoplasms; also for extraneural metastases.

Overall efficacy of antineoplastic drugs in gliomas is only modest!

- chemotherapy usually is administered on INPATIENT basis.
- in children < 3 yrs., chemotherapy is used:
 - a) instead of radiotherapy
 - b) to compensate for reduced-dose radiotherapy

N.B. full-dose irradiation is only treatment with realistic potential for long-term survival in recurrent disease.

Most chemosensitive tumors:

- 1) PRIMARY CNS LYMPHOMA – most sensitive!
- 2) OLIGODENDROGLIOMA – most sensitive of gliomas.
- 3) MEDULLOBLASTOMA, GERM CELL TUMORS

CAUSES OF CHEMOTHERAPY FAILURE

(only ≤ 10% malignant astrocytomas have meaningful and durable responses to chemotherapy):

1. **Inadequacy of drug delivery** (restricted BBB permeability* + slower blood flow in tumors**)
 - *restricts entry of water-soluble drugs
 - **reduces delivery of lipid-soluble drugs

If BBB did not exist, CNS toxicity rather than myelotoxicity or GI toxicity would be dose limiting for most drugs.

- many infiltrative primary CNS tumors have regions with apparently intact capillaries (actual extent of capillary breakdown accounting for contrast leakage is small): initially advancing tumor margins parasitize normal CNS capillaries → abnormal tumor-induced neovessels dominate established tumor areas.
- drugs can be toxic to CNS if given systemically at extremely high doses to circumvent BBB. *see below*
- delivering drugs regionally produces greater drug exposure. *see below*
- corticosteroids decrease, high-dose radiation increases transcapillary transport of BBB.

Avoid corticosteroids during chemotherapy!

2. **Tumor cell heterogeneity** (i.e. differences in chemosensitivity) → cellular resistance.
3. **Inherent resistance** - within single tumor multiple mechanisms are operating;
 - P-glycoprotein** - coded by **multidrug resistance (MDR1) gene** (chromosome 7).
 - part of BBB - "pumps out" chemicals that are potentially harmful to brain.
 - present in membrane of cancer cells and endothelial cells of gliomas.
 - little evidence links MDR1 expression with response to specific chemotherapeutic agents.
 - Methylguanine methyltransferase (MGMT)** (chromosome 10) - repairs nitrosourea-induced DNA damage, by catalyzing transfer of methyl group from guanine to its own molecule (since acceptor site cannot be regenerated, MGMT is "suicide" enzyme).
4. Large number of **nonproliferating tumor cells** (e.g. NEUROBLASTOMA).

MEASURES TO ENHANCE EFFECTS

HIGH-DOSE SYSTEMIC THERAPY

- extremely high doses to circumvent BBB.
- often with *autologous bone marrow rescue*.
- frequent **CNS & systemic toxicity!**
- tumors that benefit:
 - 1) tumor shows sensitivity to conventional-dose treatment.
 - 2) minimal residual disease after prior therapy.
 - 3) relapsed disease with minimal or no prior chemotherapy.
 - 4) pediatric brain tumors.

REGIONAL THERAPY

1. **Intra-CSF therapy** (usually by ventricular reservoir).
 - for neoplasia in subarachnoid space.
 - associated with **high morbidity rate** - commonly used drugs (methotrexate, cytarabine, thiopeta) produce CNS damage ranging from fever & chills to leukoencephalopathy & myelitis.
 - **limited efficacy in:** gross lesions (> 5 mm diameter), blocked CSF pathways.
2. **Intraarterial infusion** (through carotid or vertebral arteries) - increased drug uptake during first passage through tumor capillaries.
 - **systemic toxicity is almost not reduced** (actual amount of drug taken up into tumor is small fraction of injected dose), and **focal brain & retinal* toxicity is increased**.
 - *H: place intraarterial catheter in ICA beyond origin of ophthalmic artery
 - drugs that have **high systemic clearance** but otherwise **penetrate tumor well** are best candidates (nitrosoureas, cisplatin).
 - **nonuniform local mixing** of drug and blood at infusion site can lead to separate stream within flow of vessel ("streaming").
 - N.B. **intra-arterial BCNU** lessens survival over that afforded by **intravenous BCNU**
3. **Intratumoral therapy** - for cystic tumors with narrow rim of surrounding tumor.

BBB DISRUPTION

- reversible opening of BBB with intracarotid **hyperosmolar infusions** (mannitol, arabinose).
- can enhance penetration of different compounds of various sizes, molecular weights, and liposolubility (increased drug levels in CNS have been documented).
- produces far greater increase of entry into normal brain tissue, rather than tumor → **enhanced CNS toxicity** (similar to regional therapy).
- **leukotriene C4** increases vascular permeability in systemic capillary beds and brain tumors but has little effect on normal brain capillaries.
- other unsuccessful approaches for BBB disruption - **dimethylsulfoxide**, **hypercapnia**, low-dose ionizing or microwave **radiation**.

DIFFERENTIATION THERAPY

- differentiating agents may induce differentiation and suppress growth of tumors (incl. *GLIOBLASTOMA MULTIFORME*, *MEDULLOBLASTOMA*):

1. **RETINOIC ACID** - modulates autocrine growth loops, inhibits kinase activity of epidermal growth factor receptor.
2. **PHENYLACETATE** - DNA hypomethylation with secondary alterations in cycle-regulatory proteins.

DRUGS

- must have ability to cross BBB! (esp. for peripheral areas of tumor in which BBB is relatively intact).

All non-sugar-containing chloroethylnitrosoureas (CENUs) can cross BBB:

- 1) **CARMUSTINE (BCNU)** - most effective and most frequently used drug for *MALIGNANT ASTROCYTOMAS*.
 - special form - **Gliadel® implant** (polifeprosan 20 with carmustine) - *slow release* (over 2-3 wk) of carmustine from intraoperatively implanted biodegradable polymer wafer; up to 8 Gliadel wafers are implanted in cavity (modest benefit).
- 2) **LOMUSTINE (CCNU)**
- 3) **PCNU**
- 4) **NIMUSTINE (ACNU)**
- 5) **SPIROMUSTINE** - designed specifically for gliomas.

DIAZIQUONE (AZQ) - designed specifically for gliomas.

CARBOPLATIN - most active platinating agent.

Standard therapies:

- A) **CARMUSTINE** - drug of choice for malignant gliomas.
- B) **PCV combination (PROCARBAZINE, LOMUSTINE, VINCRISTINE)** - unusually beneficial against *OLIGODENDROGLIOMAS*.

TEMOZOLOMIDE (Temodar®) – oral alkylating agent.

- **prodrug** - rapidly spontaneously hydrolyzed to active **3-methyl(triazene-1-yl) imidazole-4-carboxamide (MTIC)**.
- mechanism of action – **DNA alkylation** (methylation mainly at O⁶ and N⁷ positions of guanine).
- oral capsules: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg.
- rapidly and completely absorbed after oral administration (100% bioavailable).
- 35% crosses BBB.
- rapidly eliminated (T_{1/2} ≈ 1.8 hr).
- drug interactions: VALPROIC ACID decreases clearance of temozolomide by ≈ 5%.
- indications:
 - 1) adult patients with **newly diagnosed GLIOBLASTOMA MULTIFORME** **concomitantly** with radiotherapy and then as **maintenance** for additional 6 months.
N.B. prophylaxis against *Pneumocystis carinii pneumonia* is required for all patients!
 - 2) adult patients with **refractory ANAPLASTIC ASTROCYTOMA** (i.e. disease progression on drug regimen containing NITROSOUREA and PROCARBAZINE).
- adverse reactions:
 - 1) **nausea & vomiting** – most common adverse events.
 - 2) **fatigue, headache**.
 - 3) **convulsions**.
 - 4) **myelosuppression** (esp. women and elderly) - prior to dosing, patients must have absolute neutrophil count (ANC) > 1.5 x 10⁹/L and platelet count > 100 x 10⁹/L → CBC on day 22 (21 days after first dose) and weekly until ANC is above 1.5 x 10⁹/L and platelet count exceeds 100 x 10⁹/L.

COMPLICATIONS

- 1) **acute encephalopathy**
 - 2) **chronic leukoencephalopathy** (bilateral periventricular white matter lesions)
 - 3) **stroke-like** episodes
 - 4) **cerebellar syndrome**
- toxicity depends on:
 - 1) dose
 - 2) route of administration
 - 3) prior radiotherapy (increases BBB permeability); e.g. methotrexate after radiotherapy!!!
 - clinical worsening may occur early in therapy (at least 10% patients) from **increase in tumor bulk** resulting from effective therapy:
 - 1) **cell mass increase** when doomed cells form giant cells or undergo one or more successful cell divisions before dying.
 - 2) **edema** caused by irritative products of cell lysis.
 - 3) CNS has **inefficient mechanism for disposing** of dead cells.

IMMUNOTHERAPY

also see p. 1675 (8) >>

N.B. CNS is immunologically isolated from immune effectors (disruption of barrier in tumors may still be insufficient to mount true response)

1. **BIOLOGIC IMMUNE RESPONSE MODIFIERS** – **VARIOUS CYTOKINES** (interferons, interleukins, tumor necrosis factor, growth factors) - demonstrate growth-inhibitory and cytotoxic responses in glioma cell lines.
2. **ADOPTIVE IMMUNOTHERAPY** (IL-2 administration with lymphokine-activated killer [LAK] cells or tumor-infiltrating lymphocytes [TILs]) - in vitro activity against gliomas; cerebral edema induced by local inflammatory response remains problem.
3. **MONOCLONAL ANTIBODIES (mAb)**
 - only few tumor-specific proteins have been identified (**truncated form of EGFR** represents unique tumor antigen on gliomas cell's surface). *see below >>*
 - most useful clinically are antibodies capable of detecting **oncofetal proteins** in tumor tissue.
 - two potential mechanisms:
 - a) **inhibition of growth-stimulatory receptor** by binding of mAb.
 - b) conjugating mAb to **cytotoxic agents** (drugs, radioactive isotopes, toxins).
 - has many problems:
 - 1) BBB is sufficiently intact to prevent easy penetration of large-molecular-weight substances (H: BBB disruption, intrathecal application).
 - 2) tumor heterogeneity
 - 3) rapid immune antibody clearance (H: human-derived antibodies, chimeric mAbs [mouse/human constructs]).

- 4) dehalogenation → loss of radionuclides (^{131}I) (H: nonhalogen radionuclides, immunotoxin-conjugated monoclonal antibodies).
- 5) excessive radiation to nontarget reticuloendothelial, hepatic, and renal tissues.

MOLECULAR SIGNATURES of Glioblastoma Multiforme

- present in all GBM cases, but not in normal CNS, i.e. common molecular denominators of GBM.

- therapeutic agents are delivered LOCOREGIONALLY (stereotactic catheter).
 - median survival increased to 360 days (vs. 84 days with Gliadel).
1. **IL-13 receptor type $\alpha 2$ (IL-13R $\alpha 2$)** – gene is found in 100% GBM cases, but protein expressed only in 75%; therapeutically used ligand – **IL-13** conjugated with **Diphtheria toxin**.
 2. **Ephrin A2** – type of tyrosine kinase in cell signaling pathways; therapeutically used ligand – **Eph A2** conjugated with **Pseudomonas toxin**.
 3. **Fra-1**

GENETIC THERAPY

see also p. 3788 >>

- extensive tumor heterogeneity - which gene(s) is to be targeted?
- all cells in tumor must be altered while sparing normal cells.
- neurons are nondividing cells and are therefore resistant to viral vectors that infect only dividing cells.

ANTISENSE REAGENTS

- pairing with complementary strand of nucleic acid → specific disruption of target gene expression.

Three different classes:

- 1) **antisense oligodeoxynucleotides (ODNs)** - short nucleotide sequences (usually < 30 nucleotides) complementary to target mRNA; effects are transient, unless ODNs are supplied continually to cell(s).
- 2) **antisense RNAs**; common production route is introduction of encoding antisense DNA gene into cultured cells or germ lines.
- 3) **ribozymes** - antisense RNAs that also have enzyme activity (cleave RNAs at preselected sites).

GENE THERAPY

- **gene transfer** (single gene could modify tumorigenic properties of cells!).
1. **Tumor-suppressor gene therapy** - replacement with correct copy of gene whose mutation initiates or significantly alters malignant phenotype (e.g. transduction of cancer cells with *p53*).
 2. **Suicide gene therapy** - transduction of gene* that converts pro-drug into toxic substance → "bystander effect" (i.e. killing of adjacent tumor cells by transfer of activated drug).
 - a) *E. coli cytosine deaminase* converts 5-fluorocytosine (5-FC) into **5-FU**.
 - b) *herpes simplex thymidine kinase (HSV-tK)* phosphorylates **GANCICLOVIR**, thus inhibiting DNA synthesis and killing cell (bystander effect is mediated through gap junction transport of nondiffusible phosphorylated GCV to nontransduced cells, and when nontransduced cells endocytose debris containing phosphorylated GCV from dying cells).

*e.g. fibroblasts neurosurgically inserted into tumor bed
 3. **Immunomodulatory gene therapy** - provokes cellular immune responses; tumor vaccine, suspension of irradiated tumor cells that are transduced with cytokine gene, is injected into skin to stimulate systemic immune response against tumor-specific antigens (there are few tumor-specific antigens and it appears to work only against low tumor burden).
 - vehicle of greatest interest in delivering foreign genes into tumor cells is *retrovirus*.

TREATMENT ACCORDING TUMOR TYPE

HIGH-GRADE ASTROCYTOMAS – (partial) resection + irradiation + chemotherapy.

LOW-GRADE ASTROCYTOMAS – surgery ± irradiation (unnecessary if completely resected).

OLIGODENDROGLIOMAS:

- a) observation
- b) surgery ± irradiation (unnecessary if grossly completely resected) ± chemotherapy.

EPENDYMOMA – surgery + irradiation (to whole CNS, if CSF seeding); chemotherapy for recurrences.

MEDULLOBLASTOMA – surgery + whole CNS irradiation ± chemotherapy.

HEMANGIOBLASTOMA – complete surgical resection (if not complete → + irradiation).

MENINGIOMA (radioresistant) – usually surgically removable ± irradiation.

SINGLE METASTASIS:

- a) surgical removal + irradiation
- b) steroids + whole brain irradiation

MULTIPLE METASTASES – steroids + whole brain irradiation ± chemotherapy.

LYMPHOMA – unusually sensitive to radiation & chemotherapy; surgery has no role!

PITUITARY ADENOMA – treatment depends on tumor size and hormonal activity:

- a) observation, medical treatment
- b) surgery ± irradiation

CRANIOPHARYNGIOMA:

- a) total surgical resection
- b) subtotal surgical resection → irradiation

PINEOCYTOMA, MATURE TERATOMA – surgery.

PINEOBLASTOMA – surgery → radiation ± chemotherapy.

NONGERMINOMATOUS GERM CELL TUMORS – chemotherapy → radiation.

GERMINOMA – radiation.

EPIDERMIOID, DERMIOID – surgery.

ACOUSTIC NEUROMA, PARANGLIOMA:

- a) surgery ± stereotactic irradiation (unnecessary if completely resected)
- b) stereotactic irradiation
- c) observation

PROGNOSIS

Extra-axial neoplasm implies more favorable prognosis than does intra-axial location.

MEDIAN SURVIVAL:

LOW-GRADE ASTROCYTOMAS ≈ 7.5 yrs. (5-yr survival 25% with surgery alone, 50% with surgery + radiotherapy);

JUVENILE PILOCYTIC ASTROCYTOMA – 5-yr survival ≈ 85% (by other data, 10-yr survival > 90%); even with partial resection median survival ≈ 8 yrs.

BRAIN STEM GLIOMA - survival of only months.

HIGH-GRADE ASTROCYTOMAS ≈ 1 yr (25% patients survive 2 yrs):

ANAPLASTIC ASTROCYTOMA ≈ 18-24 months (1,5-5 yrs.)

GLIOBLASTOMA MULTIFORME \approx 10-12 months (14 weeks with surgery alone, 40 weeks with surgery + radiotherapy); 5-yr survival < 5%

Favorable prognostic variables:

- 1) lower **tumor grade** – most important!
- 2) young **age** (< 45 yr) – second most important!
- 3) better **clinical status** (Karnofsky performance index)
- 4) little or no **residual tumor** after initial resection (prognosis is worse for midline tumors - aggressive resections are difficult).

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