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STATE-OF THE-ART IN THE MANAGEMENT OF CANCER

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MEETING COVERAGE

NEW THERAPEUTIC APPROACHES IN NEURO-ONCOLOGY

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STATE-OF THE-ART IN THE MANAGEMENT OF CANCER

CANCER OF THE CENTRAL NERVOUS SYSTEM — PART II

CURRENT THERAPEUTIC APPROACHES

Cancer of the central nervous system (CNS) is a deadly disease and its management remains a challenge. Although, generally, treatment of all brain tumors has benefited tremendously from advances in neuroimaging and neurosurgery, current standard treatment of malignant brain tumors, particularly gliomas, which typically involves surgery to remove cancerous tissue followed by radiation therapy, is inadequate. Poor prognosis associated with these tumors is related to the fact that malignant glioma aggressively infiltrates into normal brain tissues, making total tumor excision impossible. Median survival time (MST) of glioblastoma multiforme (GBM) patients is less than two years, despite multimodality treatment with extensive surgical resection and adjuvant therapies using radiation and immunochemotherapy (Yoshida J, Nagoya Journal of Medical Science, 1996 Dec, 59(3-4):97-105). Also, even after a successful initial procedure, tumors often recur and typically progress rapidly, causing deterioration of neurologic function and quality of life and resulting in death within months after diagnosis.

Advances in neurosurgical technique, novel microsurgical approaches, functional neuroimaging, computer-assisted neuronavigation, endoscopic surgery, intravascular surgery and radiosurgery, now treat benign tumors successfully allowing patients to live a near normal life span with few complications. These developments, coupled with better understanding of the role of radiotherapy and chemotherapy, may result in similar outcomes in malignant CNS tumors.

SURGERY

Surgery is the initial mode of treatment for operable tumors. Open view surgery also provides a means of categorically establishing if a tumor is malignant by tissue biopsy. The goal of surgery is removal of as much tumor as possible. If the tumor is benign, adequate resection of the mass is usually sufficient to alleviate side effects and result in a cure. If the tumor is malignant, additional interventions may be necessary. Surgery may also be used in conjunction of adjuvant local treatments that require direct tumor access, such as localized chemotherapy using catheters or implants, shunts to drain excess fluid, radioactive implants, photodynamic therapy, or hyperthermia to destroy micrometastases, etc.

Various surgical techniques are used in brain tumor removal, depending on tumor type and location (Exhibit 1). In addition to conventional approaches, other newer techniques in common use include surgical laser surgery/microsurgery, and ultrasonic aspiration.

Conventional Surgery

Conventional open surgery involves a craniotomy and subsequent tumor removal. Several techniques have been devised to help surgeons minimize damage to critical areas of the brain while resecting a malignancy. Cortical localization, or brain mapping, uses a probe that passes an electrical current to gently stimulate potentially critical areas of the brain, causing a visible movement of corresponding body parts. A similar technique uses evoked potentials to measure response of a nerve by stimulating it with mianiaturized electrodes. Also, use of ultrasound or MRI scanning may provide a "real time" image that allows the surgeon to observe the invasive actions being performed. Sophisticated image-guided technologies have been developed that allow the surgeon to continuously view instrument position in conjunction with the lesion and vital brain tissues.

Stereotactic Radiosurgery

Stereotaxy provides a computerized 3-D image that maps the tumor's precise position in the brain to facilitate surgical and/or radiotherapy planning. Frameless stereotaxy is used to provide navigational guidance during surgery. Stereotaxy is also used in tumor biopsy (see FO, p 683). Stereotactic techniques are particularly useful in guiding surgical and radiotherapy procedures involving deep-seated brain tumors, such as those located in the brain stem or thalamus.

Radiosurgery has been a major new advance in the treatment of brain tumors. In stereotactic radiosurgery high-dose radiation is delivered to a small site in the brain or spinal cord by precisely focusing radiation beams to the tumor during a single treatment session. Both inoperable benign (pituitary adenomas, pineal region or acoustic neuromas) and malignant (primary, recurrent and metastastatic) tumors of the brain or spinal cord, as well as arteriovenous malformations, may be treated by radiosurgery. Radiosurgery has been successfully used to treat solitary metastases and is becoming the standard of care for small malignant tumors with well-defined borders. Radiosurgery can also be used as an adjunct to conventional microneurosurgery; after a large portion of a mass is resected, the surgically inaccessible residuum is then treated with radiosurgery.

Sterotactic radiosurgery is noninvasive, thereby avoiding the risks of hemorrhage, infection and tumor seeding (Devita, *ibid*) and with the aid of special computer planning, it also minimizes radiation exposure to normal brain tissue. Radiosurgery, however, is also associated with a significant incidence of symptomatic radiation necrosis. Other complications include cranial neuropathies, transient neurologic deficits, and malignant edema (Devita, *ibid*).

A survival advantage of 7 months was noted when radiosurgery was used in younger patients with good performance status and lower pathologic grade, small volume,

unifocal tumors (Maitz AH, etal, Int'l J Rad Onc Bio Phys 1995;32(5):1465-71). Also, when radiosurgery was used to treat patients with previously irradiated tumors, MST was 10 months in one study of 86 such patients (Shrieve DC, etal, Neurosurgery 1995;36:275). Stereotactic radiosurgery may also be used as a local "boost" following conventional radiation therapy to treat recurring tumors in patients already exposed to the maximum safe dose of conventional radiation therapy; local control rates in such cases are in the range of 90-99% (Loeffler JS, etal, JCO 1990; 8:576-582).

Stereotactic radiosurgery may also be useful in treating brain metastases. Currently, it is most often used at the time of a solitary recurrence of disease in patients who were previously treated with whole-brain radiotherapy. However, its role in newly diagnosed brain metastases has yet to be defined (Hoegler D, Current Problems in Cancer, 1997 May-Jun, 21(3):129-83).

There are several commercially available radiosurgery systems (Exhibit 1) using a variety of radiation sources, including adapted linear accelerators (LINAC), cobalt-60 sources, and even cyclotrons, in various configurations. Energy properties associated with the particle beams (protons, neutrons, or helium ions) emitted by the cyclotron make it particularly effective for ablation of small, deep-seated tumors such as a pituitary tumors. A radiosurgery installation is expensive; prices for cobalt-60 systems range from $2.0 million to $3.5 million.

RADIOTHERAPY

Millions of radiotherapy procedures are performed annually worldwide; great strides have been made in improving delivery of this therapy to make it more effective and less toxic. Radiation therapy plays a pivotal role in the treatment of brain cancer. It is used in conjunction with surgical resection in cases of an incompletely resected tumor or a tumor considered exceptionally radiosensitive, or in place of surgery for an inaccessible tumor. Most patients with primary brain tumors are treated with radiation therapy (Exhibit 2) using different methods of delivery (Exhibit 3).

One limitation of radiotherapy is damage to healthy brain tissue that may be immediate or manifest as a late-occurring life-threatening complication. In a murine study the effects of radiation on the expression of genes encoding cytokines (TNF-α/β, IL-1 α/β, IL-2, IL-3, IL-4, IL-5, IL-6 and IFN-γ), cytokine receptors (TNFr-p55 and p75, IL-1r-p60 and p80, IFN-γr, and IL-6r), the cell adhesion molecule (ICAM-1), inducible nitric oxide synthetase (iNOS), anti-chymotrypsin (EB22/5.3), and the gliotic marker (GFAP) which are known to contribute to brain damage in other model systems, were monitored over a 6-month period using a sensitive RNase protection assay (RPA). Within 24 hours of brain irradiation an acute transitory molecular response was observed involving TNF-α, IL-1, ICAM-1, EB22/5.3 and GFAP. At 2-3 months there was re-elevation of TNF-α, EB22/5.3 and GFAP mRNA levels, but only TNF-α mRNA was overexpressed at 6 months. Because these time points coincide with the time neurological abnormalities are seen after higher radiation doses, it appears that TNF-α may be involved in late brain responses to irradiation could contribute to clinical symptoms (Chiang CS, Int'l J Radiation Biology, 1997 Jul, 72(1):45-53).

Children are particularly at risk for radiation-related side effects. Treatment-related impairments have been noted such as stunted linear growth and thyroid dysfunction that vary by age at diagnosis, by radiation treatment modality and by dose and duration of radiation A positive correlation was recently observed between age at diagnosis and age at onset of puberty in children who have been treated with high-dose cranial irradiation for CNS tumors. Although frank adrenal insufficiency is uncommon after CNS irradiation, alterations in the hypothalamic-pituitary-adrenal axis do occur. However, incidence of primary hypothyroidism may be lower when newer modes of radiation therapy such as hyperfractionated craniospinal irradiation (CSI) are used (Oberfield SE, etal, Journal of Pediatrics, 1997 Jul, 131(1 Pt 2):S37-41).

A study which assessed 28 long-term survivors of childhood medulloblastoma showed that chronic white matter loss following radiation therapy contributes to cognitive deficits. Mean ages at the time of radiation therapy and testing were 9.5 years (range=2.8-16.7) and 14.2 years (range= 6.7-21), respectively. All patients were at least 2 years old when treated with radiation therapy, and had completed such therapy at least one year previously. Lower IQs were seen in children with smaller white matter volume and longer time since radiation therapy (Gajjar A, etal, ASCO97, Abs. 1843:512).

Conventional Radiation Therapy

Conventional radiation therapy usually commences one or more weeks after surgery and continues five days a week for about six weeks. It is used to treat both primary and metastatic brain cancer (Exhibit 3). Radiotherapy relieves clinical symptoms in 70% to 90% of patients with brain metastases. Whole-brain radiotherapy is routinely administered post-operatively.

Interstitial Radiation or Brachytherapy

Stereotactic interstitial radiation or brachytherapy uses either external radiation beams focused onto the tumor bed during surgery, or radioactive seeds implanted directly into the tumor site. Interstitial brachytherapy using ^{125}I and ^{192}Ir has been commonly used in clinical practice to augment radiation dose to a single area of the brain. Candidates must have good neurologic function and a performance status >70%. Well circumscribed single lesions that are peripheral in location are best suited for this mode of therapy (Devita, *ibid*). Brachytherapy is being employed in the treatment of primary GBM and was also shown to improve survival and quality of life in those with recurrent malignant glioma (Leibel SA, etal, Int'l J Rad Onc Bio Phys

Exhibit 1
Surgical and Other Ablative Techniques in the Treatment of Brain Tumors

System	Indication	Operation	Comments
Open Surgery	In open surgery, a craniotomy is performed and the tumor exposed and visually manipulated by the surgeon; approximately 20,000 open procedures are performed in the USA and 50,000 in the Triad annually for newly-diagnosed and recurrent primary brain cancer and thousands more are performed for treatment of cancer metastasized to the brain		
Stereotactic Radiosurgery			
Cobalt 60 Sources			
Leskell Gamma Knife by Elekta Instruments (Stockholm, Sweden and Atlanta, GA)	Brain tumors (benign or malignant)	Uses a single source of radiation directed through 201 ports of a collimator helmet	As of early 1998, this system was installed in 41 sites in North America and 61 sites abroad and, as of June 1997, about 26,624 benign and 22, 937 malignant CNS tumors were treated with this system worldwide. It is priced at about $3.5 million
OUR Rotating Gamma System by OUR Scientific International (New York, NY)	Brain tumors (benign or malignant); additional sites in development	Unlike static systems, it does not requires a helmet; 30 geometrically focused cobalt sources rotate to form a tapered plane of gamma rays at the target center. As they rotate, the beams enter the skull from different directions dispersing dose exposure to healthy tissues	This system, manufactured in China, is priced at about $3.2 million
UMSI Cobalt Knife by Universal Medical Systems (Bedford Hills, NY)	Designed for treatment of tumors through the entire body		UMSI acquired the rights to this system, previously known as the Cobalt Scalpel, from Nova Therapeutic Systems
Cyclotron	A cyclotron is an adapted nuclear reactor that produces particle beams of protons, fast neutrons, or helium ions; it is commonly used to ablate small, deep-seated tumors such as a pituitary tumors. It is estimated that currently there are 19 operating facilities world-wide for proton therapy and plans for new facilities are also proposed by many other institutions around the world (Tsujii H, Nippon Rinsho Japanese J Clinical Medicine, 1997 Jun, 55(6):1588-95)		
Cyclone 235 Proton Therapy System by Ion Beam Applications (IBA; Louvain-la-Neuve, Belgium)	Deep-seated tumors	235 MeV superconducting cyclotron emits a proton beam; penetration range is determined by the Bragg peak	
IBA Neutron Therapy System		Ultra-compact superconducting cyclotron that rotates around the patient	
Linear Accelerator (LINAC)	Standard source of radiotherapy (see Exhibit 3)		
SRS-2 Stereotactic Radiosurgery System incorporating the XKnife-3 Planning System by Radionics (Burlington, MA)		SRS-2 is a complete system for LINAC-based external beam stereotactic radiosurgery using sophisticated CT contouring and surface tiling algorithms, along with MRI where appropriate, to define 3-D intracranial volumes. SRS-2 automatically aligns CT and MRI data sets using image fusion that allows optimal combination of such data sets	The XKnife-3 Planning System was developed in conjunction with the Dept. of Neurosurgery at Brigham and Women's Hospital and the Joint Center for Radiation Therapy at Harvard Medical School (Boston)
CyberKnife (also known as Neurotron) by Accuray (Sunnyvale, CA)	Designed for treatment of small tumors in critical brain and spinal cord sites; may be applicable to other sites	Does not use a fixation frame; rather the system uses robotics and missile technology to transmit 102 radiation beams that pass from numerous directions through the patient's head and focus on the target	The system has not been approved by the FDA; it is now being evaluated at 5 USA sites that will treat a total of 60 patients; its estimated cost is $2 million
Novalis by BrainLAB (Heimsteten, Germany and Palo Alto, CA)		Integrated conformal radiosurgery system	Awaiting FDA approval; in partnership with Varian Associates

— continued on next page

Other Surgery			
Laser Surgery	The laser is used in addition to or in place of a scalpel in surgery; laser microsurgery, is often performed with the aid of stereotactic localization		
Ultrasonic Aspiration	Vibration from ultrasonic waves breaks the tumor into small pieces that are subsequently aspirated out of the brain		
Stereotactic-Guided Neurosurgery/Microsurgery/ Neuronavigation	Wireless image-guided surgery system combined with 3-D brain images taken with standard scanning techniques, allows the surgeon to visualize the position of the surgical implement in relation to the tumor as well as critical brain structures during surgery		
ZD Stereotactic System by Howmedica Leibinger (Freiburg, Germany and Dallas, TX)	Microsurgery, endoscopy, biopsy, radiosurgery and seed implantation	Frame-based approach integrates microsurgical retractors, fine instrumentation, and a laser guide	
Howmedica Leibinger frameless neuronavigation using the OST-REG Cranial Marker System	Large centered craniotomies, combined supra-infratentorial approaches and skull-base and staged procedures	Semi-permament implantable fudicial system consists of titanium bone screws inserted into the skull with various attachable markers	
VectorVision by BrainLAB		Consists of computer hardware and software, infrared emitting cameras and passive markers (tiny reflective spheres) attached to instruments	The system gained 510-k clearance by the FDA in July 1997; installed in over 30 sites worldwide (6 in the USA), VectorVision has been used to treat over 3,000 patients
StealthStation image-guided surgery system supplied by Sofamor Danek Group (Memphis, TN)	Brain and spinal surgery	StealthStation provides surgeons with a computer-assisted guidance system to precisely position surgical implements	StealthStation, originally developed by Surgical Navigation Technologies and subsequently acquired by Sofamor, obtained 510(k) clearance in early 1996

1989;17:1129). Unfortunately, locoregional failure is high even after brachytherapy (Shupak K, etal, Int'l J Rad Onc Bio Phys 1995;32:1167-1170). Also, brachytherapy induces symptoms (radiation necrosis) in 40% of patients requiring additional surgery (Gutin PH, Int'l J Rad Onc Bio Phys 1991;21:601-6).

In one clinical trial involving 15 children, 4 with recurrent and 11 with primary supratentorial malignant lesions, ^{125}I implants delivered 1000 cGy/day to the tumor periphery (0.5 cm beyond the boundary of enhancement on CT scans), for a total dose of 60 Gy. Two to four weeks after removal of the implants, a total dose of 66-70.4 Gy of hyperfractionated external beam irradiation was delivered, in 110-cGy fractions, twice daily, to a 3-cm margin around the implant volume. Eight of the 11 patients with newly diagnosed tumors were also treated with 48.4 Gy hyperfractionated external beam irradiation to the craniospinal axis. Regression occurred at 2 months after implantation in all 4 patients with recurrent/secondary tumors, but local progression was subsequently documented in 2 cases at 6 and 20 months post-implantation; a third patient died 6 months post-implantation with no evidence of local recurrence and 1 remained alive with no evidence of active recurrence for at least 15 months after implantation. Local control was maintained in 9 of 11 patients with primary tumors for a median of 27 months (range=15-48+); 2 local failures occurred at 5 and 7 months after implantation. Six patients remained alive without evidence of progressive disease for an MST of 23 months after implantation. No severe acute toxicities were noted, but 7 patients later developed histologically confirmed tumor necrosis (Fontanesi J, etal, Pediatric Neurosurgery, 1995, 22(6):289-97; discussion 98).

^{125}I brachytherapy has been used successfully in surgically accessible recurrent gliomas in conjunction with continuous 20-hour infusion of carboplatin (100 mg/m^2 x 5). Catheters with ^{125}I sources were stereotactically placed in 15 patients [median age 53 years (range=30-77 years)] with recurrent GBM. Early complications included headache (n=7), transient exacerbations of pre-existing neurologic conditions (n=5), seizures, nausea or vomiting (n=2), myelosuppression (n=2), and a CSF leak at the site of the catheter wound (n=1). Late complications included steroid dependency (n=10), carcinomatous meningitis in association with hydrocephalus (n=1), and radiation-induced necrosis requiring reoperation (n=6). MST was 10 months. Three patients (2 CR and 1 PR) were still alive at a median follow-up of 31 months [Chamberlain MC and Kormanik P, American Neurological Association 1997 (ANA97), Abs. M152:67].

International Isotopes (I^3; Denton, TX), in October 1997, entered into co-operative ventures with the University of Texas M.D. Anderson Health Sciences Center, as well as several other leading universities, to advance domestic production of radioisotopes and radiopharmaceuticals for nuclear medicine research and development. In February 1998, I^3 signed an agreement with M.D. Anderson Cancer Institute to provide labeling of proprietary ^{125}I seeds used in brachytherapy for prostate cancer

Exhibit 2
Estimated Radiation Therapy Cases of Primary CNS Cancer by Major World Regions

	USA (#)	North America (#)	Europe[1] (#)	Japan (#)	Triad[2] (#)	(%)
Incidence	17,600	19,770	24,370	4,785	48,925	
Radiotherapy cases	15,365	17,259	21,275	4,177	42,712	87.3
2-year survivors	4,978	5,592	6,893	1,353	13,839	32.4
5-year survivors	3,595	4,039	4,978	977	9,994	23.4
Total brain and CNS cancer cases						
1-year survivors	7,040	7,908	9,748	1,914	19,570	40.0
2-year survivors	5,984	6,722	8,286	1,627	16,635	34.0
3.5-year survivors	5,174	5,812	7,165	1,407	14,384	29.4
5-year survivors	4,365	4,903	6,044	1,187	12,133	24.8
Prevalence						
Progressive or stable disease3	30,203	33,927	41,820	8,211	83,958	
Radiotherapy treated cases	25,854	29,041	35,798	7,029	71,868	85.6
2nd radiotherapy regimen	8,738	9,816	12,100	2,376	24,292	33.8
3rd radiotherapy regimen	262	294	363	71	729	3.0
Total radiotherapy treatments	34,854	39,152	48,261	9,476	96,889	

[1]Excluding the former USSR

[2]Triad includes North America, Europe[1] and Japan

[3]Prevalent cases of brain and CNS tumors which have not been cured

Note: Radiotherapy is also used for most cases of brain cancer metastases (see FO, p 689) of other primary tumors. Probably as many as 70% of patients with such brain metastases are treated with radiotherapy

Source: Statistics are based on standard treatment for major histology type reported by the NIH, National Cancer Institute and Central Brain Tumor Registry of the United States, 1995 Annual Report, 1996 and incidence and mortality data from Parkin DM, etal, Cancer Incidence in Five Continents, Vol.VI. IARC Scientific Publication 120; WHO, 1995 World Health Statistics Annual Report; and CA: A Cancer Journal for Clinicians 1997; 47(1):8-9 (see FO, Nov/Dec; Volume 3 #8/9)

and other diseases. This agreement will provide I[3] with certain exclusive rights to technology and patents which will be used in the production and marketing of these seeds. I[3] is also developing instrumentation for radiation therapy and medical imaging.

Boron Neutron Capture Therapy (BNCT)

Boron neutron capture therapy (BNCT) uses neutrons emitted by nuclear reactors to destroy cancer cells (Exhibit 3). BNCT was attempted in the USA in the late 1950s but failed; patients treated with low doses of neutrons died of their cancer and those exposed to higher doses died of treatment-related complications. However, BNCT had been used in Japan since 1968 and re-emerged in 1994 in the USA, despite reservations from the oncology community. BCNT is also being attempted in Europe in the European Demonstration Project for BNCT (Pignol JP, etal, Bulletin du Cancer, Radiotherapie, 1996, 83 Suppl:201s-6s).

In order for BNCT to be effective, boronated compounds must selectively concentrate in tumor cells. This is possible despite the blood brain barrier (BBB) because sometimes tumors cause a breakdown of this barrier. Also, there must be a sufficient number of thermal neutrons delivered to each of the boronated cells in the tumor bed (Moss RL, etal, J Neuro-Oncology, 1997 May, 33(1-2):27-40). Originally BNCT treatment used sodium borocaptate (BSH) but a newer compound, p-boronophenyalanine (BPA), appears to be more suitable. Also, higher energy neutrons now allow treatment through the intact skull.

Application of BNCT is currently limited by the fact that the only source of neutrons are nuclear reactors. Accelerators may also be adapted to use with BCNT but both of these sources are highly specialized expensive systems rarely found in or near hospitals. Currently, BNCT is being clinically evaluated at Brookhaven National Laboratory (BNL) and the Massachusetts Institute of Technology (MIT) and at the HFR Unit, JRC-IAM, European Commission (Petten, The Netherlands). The current clinical trials at BNL and MIT use nuclear fission reactors as neutron sources to treat GBM and deep-seated melanoma, respectively. A phase I/II trial (Protocol IDs: BNL-CIRC-266, NCI-V96-0847) is ongoing at BNL with a plan to accrue 28 adults (14 per BNCT field stratum) with GBM. The protocol involves dose increase of BPA-fructose complex from 250 mg/kg to 495 mg/kg plus either single-field (2.2 Gy-Eq to 3.3 Gy-Eq) or double-field (5.0 Gy-Eq) BNCT. Results from these trials may determine the future of BCNT. If promising, additional research will undoubtedly produce more suitable boron-labeled compounds for brain tumors. Also, optimal compound delivery and neutron irradiation will undoubtedly make BNCT a more effective treatment for brain cancer.

Boron Biologicals (BBI; Raleigh, NC) is currently producing both boron-enriched BPA and BSH under Drug Master Files submitted to the FDA. BBI is supplying BPA

to BNL and others in the USA and both BPA and BSH to European and Japanese BNCT researchers.

Radiosensitizers

Encouraging results have been reported with several agents that may circumvent radioresistance that often compromises effectiveness of radiation in malignant gliomas.

Cisplatin or carboplatin may be useful not only for their antitumoral activity against gliomas, but also as tumor radiosensitizers.

Etanidazole (Radinyl; Linz-Roberts), a hypoxic cell sensitizer, was originally developed by SRI International (SR-2508) under an NCI (NSC-301467) contract. It was subsequently licensed to Roberts Pharmaceuticals (Eatontown, NJ) and Nycomed Pharma (Princeton, NJ) which, in 1985, formed a 50/50 joint venture, Linz-Roberts, to develop the drug. Linz-Roberts was granted an exclusive license to distribute Radinyl in the USA, Canada, the UK and Ireland, and Nycomed Pharma elsewhere.

Etanidazole is currently being investigated by the NCI in a phase Ib clinical trial (RTOG-9502) in combination with radiosurgery for recurrent primary brain tumors or CNS metastases. The drug is also being investigated as a chemosensitizer and in conjunction with brachytherapy. In a phase I study of etanidazole plus radiotherapy, performed at the Joint Center for Radiation Therapy, Brigham and Women's Hospital, Harvard Medical School (Boston, MA) involving 69 patients (GBM=50 and AA=19), 14 patients were treated with interstitial implantation, in addition to accelerated fractionation radiotherapy and a continuous infusion of etanidazole. MST of GBM patients was 1.1 years and of AA patients was 3.1 years. In GBM, KPS >80, interstitial implantation, and age ≤49 did not correlate with improved survival. Etanidazole with accelerated radiotherapy produced survival results comparable to studies using BUdR, IUdR, or PCZ, CCNU, and vincristine in patients with AA but not with GBM (Chang EL, etal, Int'l J Rad Onc, Bio, Phys, 1998 Jan 1, 40(1):65-70).

Gadolinium texaphyrin (Gd-Tex), under development by Pharmacyclics (Sunnyvale, CA), is a radiation sensitizer that is selective for tumors and is detectable by MRI (see FO, p 647). In a multicenter phase Ib/II clinical trial (final enrollment was completed in mid-1997) involving patients with brain metastases, 10 daily IV injections of Gd-Tex were administered, each followed by whole brain radiotherapy (10 fractions for a total of 30 Gy). In the first 18 patients (9 male and 9 female) with 2-5 brain metastases from lung cancer (n=15), breast cancer (n=2) and thyroid cancer (n=1) enrolled in this trial, the daily Gd-Tex dose was escalated in 5 cohorts from 0.25 to 1.8 μmol/kg. Tumor selectivity of Gd-Tex was established using MRI, which showed selective drug uptake in metastases, but not in the normal brain. Among 6 evaluable patients, there were 2 CR, 3 PR, and disease stabilized in one. Overall, treatments were well tolerated (Carde P, etal, ASCO97, Abs. 1388:389).

In October 1997, results of a completed phase Ib dose-escalation study were presented at the annual meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO) in Orlando, FL. Among 39 patients with brain metastases from such primary tumors as lung cancer (n=26), breast cancer (n=6), melanoma (n=4) and other (n=3) treated under the protocol described above, the dose-limiting toxicity (DLT), occurring at 7.3 μmol/kg, was reversible elevation of liver enzymes. There were no infusion-related toxicities. MRI scans showed selective accumulation of Gd-Tex in brain metastases but not in normal brain tissue. An intent to treat survival analysis performed to compare low and higher drug dose groups with similar prognostic features, indicated that MST in the low-dose group (n=9), was 66 days compared to >363 days in the higher-dose group (n=30). Eighteen patients died in the study, 13 of tumor progression outside the brain, 4 of unknown causes, and 1 of tumor progression in the brain. As of December 1997, Pharmacyclics had enrolled 15 of the up to 20 patients to be studied in the phase II portion of this clinical trial.

Halogenated pyrimidine analogs compete with thymidine in the biosynthesis of DNA replacing a significant portion of thymidine in the DNA of actively dividing cells. Halogenated pyrimidine-substituted DNA is more sensitive to ionizing radiation because of generation of reactive intermediates and inhibition of DNA repair. Tumor cells exposed to halogenated pyrimidine analogs become 2-3 times more sensitive to radiation. Broxuridine (BUdR, Broxine) and idoxuridine (IUdR) are being developed by NeoPharm (Lake Forest, IL); under terms of a CRADA that expired May 1, 1997, NeoPharm has exclusive rights to data generated by the NCI on BUdR and IUdR for metastatic brain cancer and astrocytomas. In early 1996, NeoPharm obtained orphan drug status for use of BUdR in malignant gliomas and in 1997 filed an NDA for treatment of malignant glioma. In a related development, FDA's oncologic drugs advisory committee (ODAC) declined approval of BUdR (Neomark) as an *in vitro* prognostic in breast cancer (see FO, p 464) because of insufficient proof of clinical utility.

BUdR has been investigated clinically by the NCI since 1964. In several phase I and II clinical trials involving approximately 200 patients, conducted under the sponsorship of the NCI, BUdR, when used in conjunction with radiation therapy, has been shown to improve survival for astrocytoma patients by an additional three years, on average, compared to use of radiation therapy alone. Survival periods longer than five years have been observed in some patient groups. Increases in survival of approximately three to four months were observed in GBM patients. In a clinical trial involving 22 patients treated with BUdR and radiation, BUdR (0.8 mg/m^2) was administered weekly as a daily 96-hour infusion during a 6-week period of radiation followed by one year of PCV chemother-

Exhibit 3
Radiotherapy Techniques in Clinical Use

Radiotherapy Technique	Indication	Operation
External beam photon	Supplied by the LINAC irradiation which delivers a single, external high-energy beam collimated to reach the tumor; the system circles the patient lying on a sliding bed and directs arcs of radioactive photon beams through a collimator at the tumor; the pattern of the arc is computer-matched to the tumor's shape and radiation dose may be adjusted by degree during treatments and, by moving the patient under computer control, flexible positioning can be achieved so that more than one hemisphere is irradiated during a single treatment. Leading supplier of clinical radiation therapy systems is Varian Oncology Systems (Palo Alto, CA) having placed in excess of 3,400 radiotherapy systems worldwide; Varian systems include the Clinac LINAC among other systems and accessories. Other suppliers include Siemens Medical Systems, Oncology Care Systems (Concord, CA) which supplies the Mevatron Primus LINAC and GE Medical Systems (Waukesha, WI)	
3-D conformal radiation	Can treat multiple tumors simultaneously	Conformal radiation, a relatively new technique, uses linear (flat) high-dose radiation beams "conformed" to match the tumor's shape; these beams, emanating from a LINAC, are selectively blocked by computer-customized collimators, blocks, wedges, etc.
Intensity-modulated radiation therapy (IMRT)	Tumors near critical areas and re-treatment after maximum conventional radiation therapy failure	A type of conformal radiation, it allows varying doses of radiation from many beams of different intensity, emanating from digital LINACs, to focus on brain lesions while sparing healthy tissue; developers include treatment planning and delivery systems (the Peacock System) supplier Nomos (Pittsburgh, PA), Varian which can upgrade its Clinac system and also supplies Clinac EX, and Siemens
Hyperfractionated radiation	Indications include brain metastases	In hyperfractionated radiotherapy more smaller-than-usual daily doses are used in order to deliver higher total doses of radiation. Brief treatment schedules (e.g., 2000 cGy in five fractions over one week) are as effective as more prolonged therapy
Stereotactic radiotherapy/ stereotactic conformal radiotherapy and fractionated stereotactic radiotherapy	Indications include malignant lesions >4 cm in diameter or those that are located adjacent to critical radio-sensitive structures	Involves delivery of high-dose concentrated radiation, similar to radio-surgery, but in multiple sessions; multiple noncoplanar arcs which intersect at the target area are used to minimize dose to normal brain tissue
Intracavitary/ intraoperative radiation		A large dose of external radiation is directed at the exposed tumor and surrounding tissue or radiation is delivered in the tumor bed during surgery
Image-guided radiotherapy (also see Exhibit 1)	Deep-seated brain tumors ranging in size from 5 to 60 millimeters in diameter	Similar to image-guided surgery but for radiotherapy
External beam proton or heavy particle radiation	Requires cyclotron (sychrotron) accelerators; installations of such systems in the USA are at Loma Linda University (CA) and Harvard University (Boston, MA) and a new site will be operational at Massachusetts General Hospital (Boston, MA) in the fall of 1998	
Interstitial Radiation or Brachytherapy	Brachytherapy uses radioactive seeds implanted directly into the tumor site; various radioisotope sources have been used including iodine-125 (^{125}I), cesium-137 (^{137}Cs), iridium-192 (^{192}Ir) and palladium-103 (^{103}P)	
Boron Neutron Capture Therapy	GMB and AA	BCNT takes advantage of nuclear fission that occurs when nonradioactive boron-10 absorbs thermal or slow neutrons emitted by a nuclear reactor and, in turn, generates high linear energy transfer (LET) particles such as α particles and lithium nuclei that destroy tumor cells

apy comprising BCNU (110 mg/m^2) on day 1, procarbazine [(PCZ, Matulane; Roche (60 mg/m^2)] on days 8 to 21 and vincristine (1.4 mg/m^2) on days 8 and 29 (Leaven, etal, Int'l J Rad Onc Bio Phys 1995;32:75). Six-year survival and progression free survival were 79% and 63%, respectively (Devita, *ibid*) which was an improvement when compared to reported survival rates for low-grade gliomas. In an earlier phase II trial clinical trial, conducted by the Northern California Oncology Group (NCOG), BUdR and radiation therapy resulted in an MST of 272 weeks in anaplastic astrocytoma (AA) and 64 weeks in GBM (Phillips TL, etal, Int'l J Rad Onc Bio Phys 1991;21:709-14). These results when compared to historical controls, provide encouragement for further study of halogenated pyrimidine radiosensitizers.

IUdR is also being investigated in combination with radiotherapy with and without chemotherapy. In a phase I clinical trial of continuous IUdR infusion combined with accelerated hyperfractionated radiotherapy, patients were treated with escalating doses of IUdR ranging from 100 mg/m^2 to 400 mg/m^2 for 28 days. External beam radiotherapy involving a total dose of 70 Gy, started 7 days after drug initiation. Between June 1994 and June 1996, 16 patients (GBM=14 and AA=2) of a mean age of 52.6 years

were enrolled. Grade 2-3 toxicities included thrombocytopenia (n=2), elevated AST and diarrhea (n=1). All toxicities (except one case of thrombocytopenia) were in the 400 mg/m^2 group. As of mid-1997, 2 patients were being treated with IUdR (500 mg/m^2) without toxicities and MDT had not been reached (Schulz, CA, etal, ASCO97, Abs. 882:249a).

In another phase I clinical trial, 27 surgical patients with malignant gliomas (AA=9 and GBM=18) were treated with escalating doses of continuous infusion IUdR (125 mg/m^2 to 500 mg/m^2/day for 5 days on weeks 1 and 4) and 5-FU (300 mg/m^2/day x 7 weeks), combined with oral hydroxyurea (500 mg *q* 12 hours x 11), and radiotherapy (median dose was 62 Gy, ranging from 49.5 66 Gy). Nineteen patients were also treated with a PCV regimen. Median follow-up was 12.6 months. The 3-year progression free and cause-specific survival was 5.1% and 19.5%, respectively. Grade 3-4 toxicities were neutropenia (44%), thrombocytopenia (33%), stomatitis (30%) and infection (37%). IUDR dose intensity >150 mg/m^2/cycle was associated with a higher incidence of Grade 3-4 thrombocytopenia (50% compared to none) and infection (55.6% versus 11.1%). This regimen was associated with moderate to severe toxicity (Sweeney PJ, ASCO97, Abs. 1407:394a).

Neu-Sensamide, a neutralized formulation of metoclopramide, under development by OXiGENE (New York, NY and Lund, Sweden), inhibits DNA repair activity and induces apoptosis. The drug is administered subcutaneously. A phase I/II clinical trial, to enroll 15 patients, initiated in August 1996 at the University of Lund in Sweden, is evaluating the absorption rate of Neu-Sensamide in GBM tumors. A second phase I study is under the direction for the Harvard Medical School's Joint Center for Radiation Therapy, Department of Radiation Oncology (Boston, MA), in collaboration with the Dana-Farber Institute, Brigham and Women's Hospital and the Beth Israel Deaconess Medical Center (Boston, MA). Neu-Sensamide is in phase III clinical trials in the USA and Europe in non-small cell lung cancer.

Tirapazamine (Tirazone; Sanofi) is a bioreductive agent that is selectively activated to a reactive DNA-damaging species in hypoxic tumors. Originally developed by Southern Research Institute (Birmingham, AL) and subsequently licensed to Sanofi, as of mid-1997, tirapazamine was in phase II clinical trials as a radiosensitizer in brain cancer. In a single-arm, open label, multicenter phase II clinical trial of tirapazamine plus radiation therapy (RTOG 94 17), 55 patients with GBM were enrolled between January 27, 1995 and October 15, 1995. The total radiation dose was 60 Gy administered in 2 Gy fractions. Tirapazamine (159 mg/m^2), was administered IV three times per week during radiotherapy for a total of 12 doses. Of the 54 evaluable patients (mean age=54 years, range=23-76 years), 65% had a partial resection. There were two Grade 4 toxicities (one nausea and one muscle pain) and 9 patients (26%) experienced a Grade 3 acute toxicity. Overall MST was 10.6 months. Maximum follow-up was 14.4 months. Among 53 patients, 43 (81%) were alive six months after treatment and 6 of 29 (20.7%) were alive at one year (Del Rowe J, etal, ASCO97, Abs. 1373:385a).

HYPERTHERMIA

Hyperthermia is used to potentiate the effects of irradiation or chemotherapy. Thermoradiotherapy, a combination of interstitial hyperthermia and brachytherapy with ^{192}Ir, administered after a short course of conventional radiotherapy to 25 patients with malignant gliomas, increased survival; MST was 23.5 months (Stea B, etal, Int'l J Rad Onc Bio Phys 1994,30:591-600).

Researchers in Japan (Kakinuma K, etal, Journal of Neurosurgery, 1996 Feb, 84(2):180-4) are targeting chemotherapy to malignant brain tumors using thermosensitive liposomes that are microscopic vesicles containing drugs that are released effectively in response to hyperthermia. Thermosensitive liposomes containing CDDP were transplanted into the brains of Fisher rats implanted with Rous sarcoma virus-induced malignant glioma cells, in conjunction with localized brain heating. Ten days after tumor inoculation, the rats were assigned to one of six treatment groups (control, free CDDP only, hyperthermia only, free CDDP plus hyperthermia, CDDP-liposome, or CDDP-liposome plus hyperthermia). The rats treated with CDDP-liposome plus hyperthermia experienced the longest survival time and tumor CDDP levels in this group were the highest when compared to the other groups. Histopathologic examination showed that tumor cells were necrotized while surrounding normal brain tissue remained undamaged.

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) may be used in combination with surgery to ablate residual tumor. Although brain cancer is not a priority in PDT development, several trials are expected to commence in this area in 1998. One such multicenter clinical trial plans to use Photofrin, commercialized by QLT Therapeutics (Vancouver, Canada), to treat patients immediately after surgery, before the incision is closed.

Pacific Pharmaceuticals (formerly Xytronyx; San Diego, CA) is developing a boronated porphyrin compound, BOPP, as a photosensitizing drug for photodynamic therapy (PDT). BOPP is water soluble, stable, and easily formulated, and is extremely selective for tumor cells achieving much higher concentrations in tumor cells compared to healthy tissue. The company is planning to initially clinically evaluate this compound in brain cancer. BOPP may also be suitable for use with BNCT in the treatment of brain cancer. Patents on the BOPP technology have been issued in the USA, and have either been issued or applications are pending in major international markets. In June 1996, Pacific Pharmaceuticals entered into an agreement with Binary Therapeutics, a privately held company which holds certain proprietary technology in the

areas of PDT for treatment of cancer, and has an option to acquire BTI, subject to the satisfaction of certain conditions by both parties.

CHEMOTHERAPY

Chemotherapy has played only a limited role in treatment of brain cancer, in part because of limited access of many chemotherapeutic agents through the normally restrictive blood-brain barrier (BBB). However, many patients are offered chemotherapy as a last resort for palliation or to extend life (Exhibit 4). Few chemotherapeutics such as the lipophilic nitrosourea carmustine (BCNU) and the related compound lomustine (CCNU), which cross the BBB, are effective against brain cancer.

Although chemotherapeutics currently evaluated in brain tumors are primarily lipophilic because of their better passage through the BBB, water-soluble drugs may also have a role in brain cancer treatment. Also, BBB permeability may vary by brain cancer type. Based on data reported on 10 brain tumor patients who were studied with a quantitative CT method that established a blood-brain transfer constant (K1), an efflux constant (K2) and tissue plasma (Vp), and extracellular space (Ve) measurements (Groothuis et al, Ann Neurol, 1991;30:581), a study compared 45 Stage II-IV astrocytoma cases to 13 oligodendroglioma cases. In both types of gliomas, K1 and Ve increased with grade, but astrocytoma cases were consistently more permeable than oligodendrogliomas. Vp was the same in all grades, but Vp in astrocytomas was twice that in oligodendrogliomas. These studies suggest that all grades of astrocytic gliomas induce the same quantity of vessels (and twice as many as the oligodendrogliomas) and that the increasing enhancement (Ve) with grade correlates with increasing K1 (capillary permeability). However, chemotherapy currently used is much more effective for oligodendrogliomas than for astrocytomas, suggesting that without parallel chemosensitivity/ toxicity studies, permeability measurements are of limited value. Failure of many highly lipid-soluble drugs, such as the nitrosoureas, in almost all astrocytomas, illustrates the limitation of delivery alone. The converse is true, of course, and new agents of large molecular size have little possibility of clinical utility unless they can be delivered by circumventing the tumor capillary wall completely (Paleologos NA, etal, ANA97, Abs. M156).

Approved Drugs for CNS Cancer Indications

Few drugs are commercially available for the treatment of brain cancer (see Exhibit 5).

Carmustine and lomustine (BiCNU/BCNU and CeeNU/CCNU; Bristol-Myers Squibb) are marketed globally for the treatment of brain cancer, as an IV and oral option, respectively.

Gliadel wafer, an implantable system that delivers time-released BCNU into the cavity created by surgical removal of recurrent GBM, was approved in the USA in September 1996 and introduced to market in February 1997. Gliadel was developed by Guilford Pharmaceuticals (Baltimore, MD).

Exhibit 4
Estimated Chemotherapy Cases of Primary CNS Cancer by Major World Regions

	USA (#)	North America (#)	Europe[1] (#)	Japan (#)	Triad[2] (#)	(%)
Incidence	17,600	19,770	24,370	4,785	48,925	
Chemotherapy cases	9,891	11,111	13,696	2,689	27,496	56.2
2-year survivors	2,136	2,400	2,958	581	5,939	21.6
5-year survivors	1,325	1,489	1,835	360	3,684	13.4
Total brain and CNS cancer cases						
1-year survivors	7,040	7,908	9,748	1,914	19,570	40.0
2-year survivors	5,984	6,722	8,286	1,627	16,635	34.0
3.5-year survivors	5,174	5,812	7,165	1,407	14,384	29.4
5-year survivors	4,365	4,903	6,044	1,187	12,133	24.8
Prevalence						
Progressive or stable disease[3]	30,203	33,927	41,820	8,211	83,958	
Initial chemotherapy treatments	14,467	16,251	20,032	3,933	40,216	47.9
2nd chemotherapy regimen	5,671	6,370	7,853	1,542	15,765	39.2
3rd chemotherapy regimen	153	172	212	42	426	2.7
Total chemotherapy treatments	20,291	22,793	28,097	5,517	56,406	

[1] Excluding the former USSR

[2] Triad includes North America, Europe[1] and Japan

[3] Prevalent cases of brain and CNS tumors which have not been cured

Source: See Exhibit 2

Exhibit 5
Commercially Available Therapeutics for the Treatment of CNS Cancer

Generic Name ❑ Brand Name ❑ Supplier/Affiliate(s)	Description ❑ Side Effects	Indication	Dosage and Administration ❑ Pricing and Treatment Cost
Carmustine ❑ BCNU, BiCNU ❑ Bristol-Myers Squibb	BCNU, a nitrosourea, crosses the blood brain barrier because it is highly lipophilic ❑ toxicities include delayed cummulative bone marrow suppression (thrombocytopenia and leukopenia), pulmonary infiltrates and/or fibrosis, reversible hepatotoxicity and dose-related renal toxicity	Primary brain tumors (glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma) and brain metastases from other cancers	Monotherapy in chemotherapy-naive patients involves administration of 150-200 mg/m^2 by IV drip *q* 6 weeks as a single dose or divided into two doses over two successive days ❑ 270-360 mg per cycle; $251.0-$334.5 per cycle
Lomustine ❑ CeeNU, CCNU ❑ Bristol-Myers Squibb	as above	as above	Monotherapy in chemotherapy-naive patients involves a single oral dose of 130 mg/m^2 *q* 6 weeks ❑ 234 mg per cycle; $71.5 per cycle
Prolifeprosan 20 with carmustine (3.9%) ❑ Gliadel ❑ Guilford Pharmaceuticals/Rhône-Poulenc Rorer (WW marketing rights except Scandinavia) and Orion Farmos (Scandinavian licensing rights)	Gliadel consists of BCNU (3.9% concentration) co-dissolved with a specific polyanhydride polymer and formed into small wafers for implantation directly into the surgical cavity after removal of the brain tumor	Recurrent GBM	Gliadel is available as 8 wafers priced at $9,600 for one-time placement after surgery

Gliadel is based on a biodegradable polyanhydride polymer. The polymer matrix is hydrophobic, which protects incorporated chemotherapeutic agents from being degraded by the body. A broad range of organic and inorganic molecules can be incorporated into the matrix, including peptides and proteins. Also, a wide range of degradation rates (ranging from a few days to several years) can be achieved by altering the composition of the polymer; a constant rate of drug delivery is also possible. The polymer can be produced in a variety of shapes and can be made in flexible or rigid forms. To date no serious side effects occurred with this construct. Gliadel is produced by co-dissolving the polymer with BCNU and forming the resultant mixture into small wafers.

In June 1996, Rhône-Poulenc Rorer (RPR) acquired exclusive worldwide rights to Gliadel, excluding the Scandinavian countries where it is marketed by Orion Pharma (Espoo, Finland), in return of payments of $7.5 million in cash, $7.5 million in equity, $7.5 million in line of credit and $60 million in milestones. In the third quarter of 1996, Guilford received a $20 million milestone payment from RPR upon FDA approval of Gliadel. Under terms of this agreement, RPR also has the right of first offer for additional oncology products using Guilford's biodegradable polymer implant technology for local chemotherapy delivery. Guilford will manufactures Gliadel and receive royalty on sales. RPR will also provide $17 million for the development of Gliadel for treatment of brain cancer using higher concentration of BCNU.

The approved version of Gliadel consists of a wafer of about a quarter of an inch in diameter impregnated with 3.9% concentration of BCNU; the approved indication is for recurrent GBM. Seven to 8 wafers are implanted into the cavity left behind after a brain tumor is resected. These wafers, as they degrade, provide a timed release of BCNU directly into the tumor site, over a two-to-three week period, with most of the drug delivered in the first few days. In a North American randomized, controlled phase III clinical trial involving 222 surgical patients with recurrent GBM, Gliadel increased 6-month survival rate by more than 50%, from 36% with placebo to 56%. Survival rates at one year were 63% with Gliadel compared to 19% on placebo. Side effects included healing abnormalities, brain edema and local infections.

On January 14, 1998, Guilford announced the commencement of a phase III trial using Gliadel (3.9%), in conjunction with surgery and radiation in newly-diagnosed malignant glioma. The study's intent is to confirm previous results of a small phase III study that demonstrated a significant survival advantage over placebo when used with initial surgery. The randomized, double-blind, placebo-controlled study, to be conducted at 38 sites in 12 countries, will enroll approximately 200 patients.

A phase I clinical trial is being conducted by a CNS Consortium [New Approaches to Brain Tumor Therapy (NABTT)], comprised of 11 cancer centers, that is evaluating Gliadel wafers incorporating higher concentrations of BCNU. After finding a concentration of 6.5% and 10%

safe, clearance was obtained to test the ultimate concentration goal of 20%. Project leader is Stuart R. Grossman of the Johns Hopkins Oncology Center.

It is estimated that approximately 12.5%-17.5% of patients undergoing open surgery for primary brain cancer have recurrent GBM and would be candidates for Gliadel. In the USA, this estimate results in 2,500 to 3,500 candidates and a potential annual market of $25 million to $35 million and a worldwide market, based on 6,250 to 8,750 procedures, of approximately $62 million to $85 million, at the current USA price of $9,600. Gliadel is also being investigated for the indication of newly-diagnosed malignant glioma. Inclusion of such cases is expected to add 5,000 to 7,000 patients annually in the USA and 12,500 to 17,500 worldwide, adding another $125 million to $175 million in potential sales. In 1997 RPR also filed for regulatory approval in Canada, Brazil, Malaysia, South Africa and Korea.

Commercial Drugs in Clinical Trials for CNS Cancer Indications

Numerous drugs, mostly in combination and/or multimodality protocols are being evaluated in the management of CNS cancer (see Exhibit 6).

Carboplatin is active in gliomas but is limited in its ability to penetrate the BBB. However, when carboplatin delivery to brain tumors is optimized with osmotic blood-brain barrier disruption (BBBD), complete radiographic responses are obtained, particularly in PNET and germ cell tumors. Unfortunately, patients treated with this regimen may sustain high frequency hearing loss.

Other lipophilic drugs, such as the taxanes paclitaxel (Taxol; Bristol-Myers Squibb) and docetaxel (Taxotere; Rhône-Poulenc Rorer) and the topoisomerase I inhibitors, irinotecan (Camptosar; Pharmacia & Upjohn) and topotecan (Hycamtin; SmithKline Beecham) are also being evaluated in brain cancer (Exhibit 6).

Chemotherapy Delivery Options

Intra-arterial chemotherapy

Patients with metastatic brain tumors who respond poorly to standard IV chemotherapy may benefit from regional intra-arterial (IA) administration of chemotherapy that results in increased tumor uptake of drug, with improvement in response rates and survival. IA chemotherapy may increase uptake during initial infusion by allowing drugs to more efficiently enter through the BBB.

Twelve patients were treated with IA carboplatin (200 mg/m²/d) and IV etoposide (VP-16; 100 mg/m²/d) for 2 days every 3 to 4 weeks. Patients ranged in age from 32 to 68 years (mean= 50.1 years). There were 4 CRs (44%), 4 PRs (44%) and disease stabilized in 2 (22%) and progressed in 2 (22%). Mean time to progression was 25.3 weeks overall and 30.6 weeks in responders (range= 6-76 weeks). Although these results are preliminary and representative of only a small population, IA carboplatin and IV VP-16 appear to be active agents in the treatment of brain metastases (Newton HB, etal, ANA97, Abs. M157:68).

A study of IA CDDP and VP-16 for primary and metastatic brain tumors was conducted between 1987 and 1996, involving 173 patients who were treated with either CDDP (40 mg/m²) and VP-16 (20 mg/m²) or CDDP (60 mg/m²) and VP-16 (40 mg/m²); 159 patients treated with a total of 410 cycles were assessed for toxicities. The most common toxicity was nausea and vomiting (14%) and no significant differences in toxicity were noted between the two regimens. Patients with primary disease experienced a lower incidence of toxicities than those with metastases (23% versus 37%) and incidence of toxicities was higher in those who were exposed to radiotherapy prior to treatment as compared to those who were treated with radiotherapy post IA infusion (42% versus 27%). MST in GBM treated with this regimen concomitant with radiotherapy was shorter than in those treated with IA chemotherapy prior to radiotherapy (7 months versus 23 months). IA chemotherapy with CDDP and VP-16 is safe and effective, especially in radiotherapy-naive patients with primary brain cancer (Tfayli A, etal, ASCO97, Abs. 1904:528a).

Intrathecal chemotherapy (IT) is usually is the treatment of choice in meningeal cancer. Methotrexate (MTX) has become the IT drug of choice for carcinomatous meningitis resulting from solid tumor metastasis. There is equivalent efficacy between IT MTX and IT thiotepa (Thioplex; Immunex) which is used as second-line therapy (ASCO91;10:377). Cytarabine (ara-C, Cytosar; Pharmacia & Upjohn) is used to treat leukemia- and lymphoma-related neoplastic meningitis.

Thiotepa is commonly recommended as a standard treatment for leptomeningeal metastases (LM) in children. To determine the efficacy of IT thiotepa in pediatric LM, investigators reviewed all records of children treated with IT thiotepa for LM from 1980 through 1996 at the Johns Hopkins Hospital (Baltimore, MD) and Strong Memorial Hospital (Rochester, NY). All 15 patients (mean age=6.4 years, 8 males) with LM were treated with IT thiotepa using a dose range of 5 mg/m² to 11.5 mg/m² for 2-7 doses. MST from the start of IT thiotepa for all 15 children was 3.6 months; overall survival was 26.7% at 1 year. Although data from this study are confounded by simultaneous treatments as well as differing histologic diagnoses, the very few responses observed suggest only limited efficacy for IT thiotepa in pediatric LM (Fisher EG, etal, ASCO97, Abs. 1883:523).

Intrathecal melphalan (L-PAM) is being investigated at Duke Comprehensive Cancer Center for neoplastic meningitis in a phase I clinical trial (Protocol IDs: DUMC-1631-96-11R4, NCI-V96-0869) in patients aged >3 years with histologically confirmed malignancy that is metastatic to the cerebrospinal fluid (CSF) or leptomeningeal/subarachnoid space as a result of leukemia, lymphoma or germ cell tumors. At least 3 children and 3 adults will be treated at each dose studied. L-PAM is administered by an Ommaya reservoir.

Exhibit 6
Ongoing Clinical Trials with Commercially Available Chemotherapeutics for CNS Cancer

Therapy	Results	Status➢Location ❑ Tumor Type	Comments and References
Surgery + radiation + TPCH [6-thioguanine + procarbazine (PCB) + lomustine (CCNU) + hydroxyurea (HU)]; PO *q* 6-8 weeks, before and after CCNU	MST was 18 months in GBM and 28 months in AA; SR of patients with total or subtotal tumor resection was 80% and, with partial resection or biopsy, 20%	Phase III➢M. D. Anderson Cancer Center ❑ high-grade astrocytomas in children	This oral, outpatient regimen achieved survival rates comparable to more intensive inpatient regimens (Ater L, etal, ASCO97, Abs. 1889:525)
VP-16 (100 g/m^2) IV on days 1-3 + thiotepa (40-70 mg/m^2 IV on day 2 with 10 mg/m^2 increments) *q* 3-4 weeks; median total dose of thiotepa in cycle 1 was 60 mg/m^2	All patients died of progressive disease and not of chemotherapy complications	Phase I➢Columbia Presbyterian Medical Center (New York, NY) ❑ recurrent malignant glioma (all previously treated with radiation and 8/15 with BCNU)	Balmaceda C, etal, Cancer Chemotherapy and Pharmacology, 1997, 40(1):72-4
High dose BCNU (800 mg/m^2) + autoBMT	5/13 (38%) SD; one patient developed fatal respiratory distress 50 days after treatment	Phase II➢Centre Leon Berard (Lyon, France) ❑ pediatric high-grade gliomas	Bouffet E, etal, Cancer Chemotherapy and Pharmacology, 1997, 39(4):376-9
CCNU (80 mg/m^2) on day 1 + [carboplatin (80 mg/m^2) + vinorelbine (20 mg/m^2) + L-leucovorin (250 mg/m^2) + 5-FU (500 mg/m^2)] on days 1, 8, 15, 22; cycle repeated *q* 6 weeks	21.4% (6/28) PR, 35% (9/28) SD; median time-to-progression (TTP) was 3.7 months	Phase I/II➢Castelfranco (Veneto, Italy) ❑ brain metastases from breast and lung adenocarcinoma	Colleoni M, etal, Am J Clinical Oncology, 1997 Jun, 20(3): 303-307
Regimen A: cyclophosphamide (CTX; 65 mg/kg) IV on day 1 + vincristine (VCR; 0.065 mg/kg) IV on days 1, 8 Regimen B: CDDP (4 mg/kg) IV on day 1 + VP-16 (6.5 mg/kg) IV on days 3, 4; in 28-day cycles (AAB, AAB)	Secondary malignancies developed in 5/132 patients <age 2 years; 3 developed lymphoproliferative disease and 2 developed solid tumors	Phase I➢SUNY at Buffalo School of Medicine ❑ malignant brain tumors in children <age 3 years (n=198)	High rate of secondary malignancies may be the result of prolonged use of alkylating agents, VP-16 and radiation (Duffner P, etal, ASCO97, Abs. 1887:524); POG 8633
Dose-intensified PCV [IV CCNU (130 mg/m^2) on day 0 + vincristine (1.5 mg/m^2) on days 0, 7 + PCZ (150 mg/m^2) on days 1-7 + PBSC support on day 9] *q* 28 days x4; those with high-grade tumors were treated with radiotherapy after the fourth course	3/37 (8.1%) required platelet transfusion; 4 brain stem glioma (BSG) patients improved 7-10 days after treatment initiation; tumor size decreased in 7 patients	Phase II/III➢U Western Ontario (Canada) ❑ newly diagnosed gliomas [diffuse, intrinsic BSG; (n=4), focal intrinsic BSG (n=3), temporal lobe glioblastoma (n=l), anaplastic ependyrnoma (n=l) and hemispheric low-grade glioma (n=l)]	Dose-intensification of PCV was possible using PBSCs without untoward toxicity and resulted in encouraging responses in this small trial (Jakacki R, etal, ASCO97, Abs. 1435:402)
POMB/ACE (CDDP + VCR + methotrexate (MTX) + bleomycin/actinomycin D + CTX + VP-16)	Disease stabilized in 6/8 (75%) of patients at 10-44 months; treatment was discontinued in 2 because of renal failure secondary to CDDP and diabetes; CDDP was replaced with carboplatin in 5 because of renal toxicity and/or ototoxicity	Phase I➢M.D. Anderson Cancer Center, Texas Children's Hospital ❑ pediatric primary CNS mixed germ cell tumors (n=8; age 2-13)	Kuttesch JF, etal, ASCO97, Abs. 1895:526
Post-operative radiotherapy (n=361) + intra-arterial BCNU (n=153); total (n=379)	MST was 100 months; those with symptoms of expansion (n=97) survived longer when resected; projected 10 and 15 year survival was 42% and 29%, respectively	Phase III➢Norwegian Radium Hospital (Oslo, Norway) ❑ low-grade glioma	Lote K, etal, J Clinical Oncology, 1997 Sep, 15(9):3129-40
VP-16 + CTX, or ifosfamide (IFF), or carboplatin, each with G-CSF support; radiation (4-10 MeV) + VCR were subsequently administered to all and those with no tumor progression were treated with CCNU + VCR	Ongoing; 30 patients	Phase II➢multicenter [Children's Cancer Group Princess Margaret Hospital for Children (Perth, Western Australia)] ❑ pediatric newly-diagnosed high-grade astrocytomas	Protocol IDs: CCG-9933

— continued on next page

Radiotherapy using photons of 6-25 MeV followed by VCR + CDDP + CTX + VP-16	Ongoing; a minimum of 35 patients, ages 3-21	Phase II➢multicenter [Children's Cancer Group, Princess Margaret Hospital for Children (Perth, Western Australia)] ❑ pediatric newly-diagnosed intracranial ependymoma and radiologic evidence of postoperative tumor	Protocol IDs: CCG-9942
^{131}I-MIBG (100 mCi) IV day 2, 9 + CDDP (50 mg/m^2) IV day 1, 8 administered in 6 hours; additional therapy included CTX		Phase I/II➢Catholic U (Rome, Italy), U Bologna (Italy) ❑ disseminated neuroblastoma (n=5,then additional therapy, n=10)	CDDP and CTX were administered 1 week before ^{131}I-MIBG to reduce toxicity through the priming effect (Mastrangelo R, etal, ASCO97, Abs. 1897:527)
Concurrent BCNU + cranial - irradiation using Cobalt 60 or photons of greater energy versus 3 cycles of 3-day continuous-infusion of BCNU + CDDP, followed by cranial irradiation	Ongoing as of 2/96; approximately 220 patients will be accrued over 22 months	Phase III➢Southwest Oncology Group (SWOG) ❑ newly diagnosed supratentorial GBM	Protocol IDs: E-2394, SWOG-9508
BCNU versus BCNU + VCR + nimodipine	Ongoing; accrual of the required 40 patients per arm should be complete in about 2.5 years	Phase III➢EORTC Brain Tumor Cooperative Group ❑ adult recurrent malignant gliomas	Protocol IDs: EORTC-26881
G-CSF ± CTX + high-dose BET (BCNU + VP-16 + thiotepa) + PBSC support	Ongoing; to enroll up to 35 patients, ages 3-21	Phase I➢Herbert Irving Comprehensive Cancer Center (New York, NY) ❑ adult malignant gliomas	Protocol IDs: CU-7047, NCI-V96-0826
CDDP + DOX + tamoxifen	Ongoing	Phase II➢Ottawa Regional Cancer Centre (Canada) ❑ incurable soft tissue and endocrine malignancies	Antiestrogen therapy (Protocol IDs: CAN-OTT-9401, NCI-V94-0566)
MMOPP (MTX + NM + VCR + PCB + PRED)	Ongoing; ≥1 CR observed in the first 5 patients; an additional 20 patients will be entered	Phase II➢M.D. Anderson Cancer Center ❑ astrocytomas and primitive neuroectodermal tumors	Protocol IDs: MDA-P-88006, NCI-V89-0125
Local-field irradiation + high-dose carboplatin + thiotepa + autologous PBSC or autoBMT	Ongoing; 60 patients will be entered over 3 years	Phase II➢Memorial Sloan-Kettering Cancer Center ❑ GBM or brain stem tumors	Protocol IDs: MSKCC-94101, NCI-V94-0594
Standard versus dose-intense CTX + VCR + CDDP + VP-16 with or without radiotherapy	Ongoing; 330 patients will be entered	Phase III➢multicenter [Pediatric Oncology Group (POG)] ❑ children <age 3 years with a CNS malignancy	Protocol IDs: POG-9233/34, POG-9234
CTX + G-CSF or high-dose VP-16 + carboplatin + escalating-dose of CTX + autologous CD34 + PBSC rescue + G-CSF	Ongoing; at least 36 patients will be entered, 10 one one regimen and 26 on the other	Phase I➢Johns Hopkins Oncology Center ❑ neuroblastoma, PNET and germ cell tumors	Protocol IDs: JHOC-9511/9512, NCI-V95-0688
CDDP + VP-16	Ongoing; initially 12 patients in each tumor category (germinoma versus nongerminoma); if 7-11 objective regressions are seen in either group, 13 additional patients will be entered, age 3 and over	Phase II➢Mayo Clinic Cancer Center ❑ pediatric recurrent CNS cancer	Protocol IDs: MAYO-891351, NCI-T92-0208D
CDDP + VP-16; patients who achieved CR are treated with irradiation using linear accelerators with ≥4 MeV	Ongoing	Phase II➢Mayo Clinic Cancer Center ❑ CNS germ cell malignancies	Protocol IDs: MAYO-891351, NCI-T92-0208D
CDDP + VP-16 on days 1-3, repeated *q* 4 weeks for a total of 6 courses	Ongoing; a total of 35 patients will be entered over approximately 7 years	Phase II➢Mayo Clinic Cancer Center ❑ adult recurrent ependymomas	Protocol IDs: MAYO-907253, NCI-V96-1072
Liposomal cytarabine (DTC 101, Savedar or DepoCyt) versus standard therapy	Ongoing; a minimum of 120 patients will be entered	Phase III➢multicenter (Cross Cancer Institute, etc.) ❑ neoplastic meningitis	Protocol IDs: DTC-92-001, NCI-V97-1338
Liposomal cytarabine (DTC 101) *q* 14 days for 4 weeks; then DTC 101 *q* 14 days for 6 weeks, then 1 dose 28 days later	Ongoing; the study will accrue 40 patients with positive and 40 patients with negative CSF cytology	Phase III➢multicenter (Cross Cancer Institute, Toronto Hospital, U Colorado Cancer Center, John Wayne Cancer Institute, etc.) ❑ adult neoplastic meningitis and primary brain tumors	Protocol IDs: DTC-96-001, NCI-V97-1337

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Intrathecal melphalan (L-PAM, NSC-8806)	Ongoing	Phase I➢Duke Comprehensive Cancer Center ❑ pediatric neoplastic meningitis	Protocol IDs: DUMC-1631-96-11R4, NCI-V96-0869
Docetaxel + G-CSF *q* 21 days for ≤12 courses	Ongoing; 20 patients by disease category (soft tissue sarcomas, osteosarcoma, neuroblastoma, medulloblastoma/PNET, and astrocytoma/glioma) will be entered over 2-3 years	Phase II➢multicenter [Princess Margaret Hospital for Children (Perth, Australia), British Columbia Children's Hospital (Vancouver, BC)] ❑ pediatric recurrent solid tumors	Protocol IDs: CCG-0962
Radiotherapy (using linear accelerators with photon energies of ≤4 MeV) + continuous-infusion of paclitaxel escalated to MTD	Ongoing	NCI Phase I➢Simmons Cancer Center (Dallas, TX) ❑ adult GBM	Protocol IDs: UTSMC-IRB-0393-09900, NCI-T92-0250D
Paclitaxel (225 mg/m^2) IV over 3 hours, 3x + carboplatin [no improvement mandates brain irradiation (30 Gy in 10 fractions); responding patients are treated with 3 more courses of chemo-therapy + irradiation]	1/5 (20%) PR in brain and extracranial sites	Phase I➢M. D. Anderson Cancer Center ❑ brain metastases in non-small cell lung cancer	Preliminary results are consistent with the study hypothesis so new patients are being enrolled in the study (Lee JS, etal, Seminars in Oncology, 1997 Aug, 24(4 Suppl 12):S12-52-S12-55)
Paclitaxel + topotecan + G-CSF, *q* 3 weeks for ≤2 courses	Ongoing; a total of 35 patients will be entered	Phase II➢Norris Cotton Cancer Center ❑ adult recurrent GBM or AA	Protocol IDs: DMS-9607, NCI-V96-0955
Topotecan (30-minute infusion for 5 days beginning with 1.4 mg/m^2/day, then at 20% dose escalation)	MTD was 30-minute infusion for 5 days at 1.4 mg/m^2/day without G-CSF or 2.0 mg/m^2/day with G-CSF	Phase I➢M. D. Anderson Cancer Center ❑ pediatric refractory brain tumors (n=10), neuroblastoma (n=9)	DLT is hematopoietic (Tubergen DG, etal, J Pediatric Hematology/ Oncology, 1996 Nov, 18(4):352-61)
Topotecan was administered as a 24-hour IV infusion *q* 21 days; initial dose was 5.5 mg/m^2 escalated to 7.5 mg/m^2 on 2nd and subsequent doses	There was 1 PR of >17 months in low-grade glioma; disease stabilized in 3 cases of BSG for 12-28 weeks, in 1 case of malignant neuroepithelial tumor for 41 weeks and in 1 case of optic glioma for 22 weeks	Phase II➢The Pediatric Branch, NCI ❑ pediatric CNS tumors (n=45), including brain stem glioma (BSG)	Topotecan at this dose regimen was inactive in high-grade gliomas, medulloblastomas, and BSG (Blaney SM, etal, Cancer, 1996 Aug 1, 78(3):527-31)
Topotecan (infusion for 72 hours per week with dose escalations in cohorts of 3 patients to MTD) + BCNU (IV infusion over 1 hour *q* 6 weeks to MTD)	Ongoing; an estimated 18-36 patients will be entered	Phase I (12/97)➢Duke Comprehensive Cancer Center, Saint Jude Children's Research Hospital (Memphis, TN) ❑ adult recurrent primary malignant glioma	Protocol IDs: DUMC-223972, NCI-G97-1242
Arm I: irinotecan IV over 90 minutes on days 1, 8, 15, 22, then rest for 2 weeks and continue for ≤6 cycles Arm II: irinotecan on day 1 *q* 3 weeks for ≤12 cycles	Ongoing; projected accrual 30-60 patients in 15-30 months	Phase I➢NCI, North Central Cancer Treatment Group ❑ adult recurrent primary malignant glioma	NCI cooperative group program, Protocol ID: NCCTG-967251
Irinotecan (IV once weekly x4 followed by 2 weeks rest with dose escalations in cohorts of 3 patients to MTD) + BCNU (administered over 1 hour *q* 6 weeks to MTD)	Ongoing; 18-36 patients will be entered	Phase I➢NCI, Duke Com-prehensive Cancer Center ❑ adult recurrent primary malignant glioma	Protocol IDs: DUMC-461973, NCI-G97-1243
Irinotecan (CPT-11)	Ongoing; projected accrual is 30 patients per stratum (newly-diagnosed or recurrent) over 1.5-2 years; if ≤1 response is seen in the first 15 patients entered in each stratum, the study will be closed	Phase II➢NCI, Duke Com-prehensive Cancer Center, Cleveland Clinic, Saint Jude Children's Hospital ❑ newly diagnosed or recurrent adult malignant gliomas	Henry S. Friedman, Chair; Protocol IDs: DUMC-770-96-6, NCI-T95-0089D, CWRU-1396
Radiotherapy + dibromodulcitol (DBD) radiosensitization, followed by DBD + BCNU versus radiotherapy alone	Ongoing; a total of 212 patients will be entered over more than 3 years	Phase III➢EORTC Brain Tumor Cooperative Group ❑ adult anaplastic astrocytomas	Protocol IDs: EORTC-26882

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Gliadel incorporating escalating concentrations of BCNU (current level is at 20%)	Ongoing; up to 34 evaluable patients	Phase I➢Johns Hopkins Oncology Center, multicenter ❑ adult recurrent malignant glioma	Protocol IDs: JHOC-NABTT-101-9601, NCI-T96-0052H
Octreotide (daily subcutaneous injections at increasing doses for 3 days; then at MTD for ≥6 months)	Ongoing; projected accrual is 14 patients	Phase II➢NCI, Mayo Clinic Cancer Center ❑ adult meningioma and meningeal hemangiopericytoma	Protocol IDs: MAYO-917202, NCI-V96-1073
IFN-α at a dose of 6 MU as a 2-hour infusion on day 1 and at 3 MU on alternating days to day 42 + BCNU (150 mg/m^2) IV on day 1, following surgery and radiation	7/21 (33%) PR, 6/21 (29%) SD; TTP was 4.5 months and MST was 7 months	Phase II➢Azienda Ospedaliera (Padova, Italy) ❑ high-grade recurrent gliomas	Brandes AA, etal, Am J Clinical Oncology, 1997 Aug, 20(4):364-7
2 monthly cycles of CDDP (100 mg/m^2) on day 1 + IL-2 (18 MUI/m^2) as a 24-hour IV on days 3-6, 17-21 + IFN-α 2a (9 MUI) 3 times/week + 4 monthly maintenance cycles of CDDP on day 1 + IL-2 on days 15-19 + IFN-α 2a thrice weekly on days 19-26	Overall response rate (OR) was 39% (1 CR + 5 PR>50%); MST was 32 weeks (51 weeks for patients with OR)	CHU (Grenoble, France), Salpetriere Hospital (Paris, France) ❑ melanoma brain metastasis	This treatment appears to be an alternative to radiotherapy or chemotherapy alone in selected melanoma brain metastasis cases (Mousseau M, etal, ASCO97, Abs. 1773:492)
IFN-α + surgery, followed by IFN-α + BCNU or IFN-α + tamoxifen + surgery, followed by IFN-α + TMX + BCNU	Ongoing; up to 50 patients will be entered	Phase II➢Missouri Cancer Associates ❑ adult Grade III/IV and recurrent malignant gliomas	Protocol IDs: HOA-5717, NCI-V96-0890, UMC-5717
INF-α as a subcutaneous injection 5 days/week x 8 weeks	Ongoing; 20 patients will be entered per year into each arm	Phase II➢M.D. Anderson Cancer Center, U Iowa ❑ adult recurrent meningiomas	Protocol IDs: MDA-DM-96296, NCI-G97-1206
IFNβ-1a (Avonex) as 3 intramuscularinjections/week; acetaminophen was administered *q* 4 hours for 24 hours after injection	Ongoing; a maximum of 35 patients will be enrolled	Phase II➢NCI, M.D. Anderson Cancer Center, Vincent T. Lombardi Cancer Research Canter, Brigham and Women's Hospital ❑ adult recurrent gliomas or astrocytomas	Protocol IDs: MDA-NCNSC-96314, NCI-T94-0125
CTX + topotecan for 5 days + G-CSF on day 6 until hematologic recovery	Ongoing; a total of 30 patients per stratum (brain tumor versus other)	Phase II➢multicenter [POG, Clinique de Pediatrie (Geneva, Switzerland)] ❑ pediatric recurrent or refractory solid tumors	Protocol IDs: POG-9464
Tumor irradiation using megavoltage equipment (at least 4 MeV) + BCNU or + stereotactic tumor irradiation	Ongoing; 200 patients will be entered over 3 years	Phase III➢Cross Cancer Institute, Royal Prince Alfred Hospital (Sydney, Australia), multicenter study ❑ adult supratentorial GBM	Protocol IDs: RTOG-9305
HU + ara-C (as a 12-hour continuous infusion) + CDDP	Ongoing; a total of 110 patients will be entered	Phase II➢SWOG, multicenter ❑ adult malignant glioma	Protocol IDs: SWOG-9149
Intensive PCV; those achieving CR or a major PR proceed to theotepa + autoBMT	Ongoing; up to 18 patients will be entered	Phase II➢U Alabama Comprehensive Cancer Center ❑ recurrent oligodendroglial tumors	Protocol IDs: UAB-4126, NCI-V93-0284
Leukapheresis + intracavitary IL-2 + lymphokine-activated killer (LAK) cells, infused on day 1; bolus infusions of low-dose IL-2 on days 3, 5, 8, 10, and 12, rest days 13-24; repeat for up to 1 year for SD or response	2/10 (20%) PR; ongoing; 30 patients per year will be enrolled	Phase II➢Staten Island U Hospital North, Bombay Hospital (India) ❑ primary, recurrent, or refractory adult gliomas	Sankhla SK, etal, J Neuro-Oncology, 1996 Feb, 27(2): 133-40; Protocol IDs: SIUH-RP-96-004, NCI-V97-1326
High-dose IFF (2 gm/m^2/d) as a continuous IV infusion for 6 days along with mesna, followed with G-CSF, for a total of 25 cycles	Among 8 patients, 4 (3 with breast cancer) were evaluable for response and 8 for survival; 2 breast cancer patients achieved PR, both in brain and non-brain metastases, suggesting penetration of the BBB; duration of responses were 12+ and 44 weeks	Phase II➢West Virginia U (Morgantown, WV) ❑ metastatic cancer	More patients with brain metastases continue to be accrued to confirm these promising preliminary results (Khori NA, etal, ASCO97, Abs. 423:121a)

DepoCyt (DTC-101), under development by DepoTech (San Diego, CA), is a sustained-release formulation of cytarabine. DepoCyt is constructed using the company's proprietary DepoFoam technology which consists of an injectable non-toxic biodegradable material composed of microscopic lipid particles that can be used to encapsulate a wide variety of drugs with high efficiency. DepoTech has been clinically investigating DepoCyt in neoplastic meningitis since 1992.

In April 1997, DepoTech filed the initial part of a NDA for DepoCyt for the treatment of neoplastic meningitis arising from solid tumors in accordance with the rolling NDA procedure. In July 1997, the FDA accepted the company's filing based on the one pivotal phase III clinical trial of DepoCyt involving 61 patients with neoplastic meningitis arising from solid tumors. The study included a 4-week induction phase and a maintenance phase. In the induction phase, patients were randomized to either two doses of DepoCyt (50 mg) administered every two weeks, or 8 doses of MTX (10 mg) twice a week. Both groups were also administered concurrent dexamethasone to prevent chemical arachnoiditis that occurred more often (69%) in the DepoCyt group than the MTX (33%) group. Those achieving CR during this phase were treated with four doses of DepoCyt or 8 doses of MTX and followed-up for three months for adverse events and, thereafter, to determine time to disease progression and, ultimately, survival. CR was defined as no sign of cancer after the fourth week in cells taken from sites that had been positive or suspicious for malignancy at baseline, and no clinical evidence of disease progression. Using this definition, response rates were not significantly different between DepoCyt's 26% (8/31) or MTX' 20% (6/30). The median duration of clinical and cytologic response for DepoCyt and MTX was 39 days versus 26 days and 39 days versus 34 days, respectively. Median cytologic time to progression was 50.5 days for DepoCyt and 84 days for MTX and median survival of those on DepoCyt was 107 days, compared with 82.5 days for those on MTX. Only the difference in the median time to clinical progression between those on DepoCyt (166.5 days) compared to those on MTX (66.5 days) was statistically significant. One advantage of DepoCyt, cited by ODAC, is the fact that it is administered once every two weeks rather than twice a week or more often. However, there was a higher incidence of serious adverse effects with DepoCyt (83%) compared to MTX (50%), including headache, back pain and fever.

In December 1997, FDA's ODAC did not recommend approval of DepoCyt for use in patients with neoplastic meningitis from solid tumors. The majority (7-3 with one abstention) of ODAC members did not consider that the company's submission showed that DepoCyt was effective for this indication. Among the problems cited by ODAC was the small enrollment size, although it was the largest ever in neoplastic meningitis, frequent protocol changes, and the definition of a CR, among others.

ODAC members agreed that a clearer picture regarding DepoCyt's role in the treatment of neoplastic meningitis should emerge when results from phase III clinical trials which directly compare ara-C with DepoCyt in treating neoplastic meningitis arising from leukemia and lymphoma, become available. These trials were still accruing patients as of early 1998. Generally, trials with neoplastic meningitis patients are difficult to do because of the small number of affected populations and their limited survival outlook. With current treatments, life expectancy of those with neoplastic meningitis is between two and four months. In view of the short life expectancy, DepoCyt's dosing convenience became less desirable when juxtaposed with the agent's more serious side effects when compare to MTX. Because these treatmens are palliative rather than curative, increased toxicity results in poor quality of a patient's remaining short lifespan. Also, ease-of-administration may induce oncologists to recommend treatment in cases where it would result in no significant benefit. Such cases are probably not offered treatment currently.

A phase IV non-randomized trial in solid tumor patients and a dose-escalating clinical trial in pediatric patients were ongoing as of August 1997. Also, in January 1998, a Marketing Authorization Application for Savedar, the European trade name for DepoCyt, was submitted to the European Medicines Evaluation Agency.

In March 1994, DepoTech entered into a collaboration with Chiron regarding development of proprietary DepoFoam formulations of certain generic compounds including DepoCyt, for the treatment of cancer, as well as of certain cytokines, vaccines, growth factors and selected gene therapy products proprietary to Chiron. At that time, Chiron made a $2.5 million equity investment in DepoTech and paid $1.0 million for a warrant which was converted in January 1995 to a DepoCyt marketing rights fee. In 1995 Chiron made a $3.5 million payment to DepoTech upon achievement of a development milestone, for Chiron's share of DepoCyt's clinical trial and development costs from July 1993 through December 1994 and continues to share equally in such costs associated with DepoCyt's development in the USA. DepoTech may receive additional payments upon achievement of certain other developmental milestones. In June 1997, DepoTech announced the repurchase from Chiron of rights to DepoCyt in Canada and Europe for $13.7 million. Chiron retained exclusive rights in the USA.

In July 1997 DepoTech signed of an agreement under which Pharmacia & Upjohn will market and distribute DepoCyt outside the USA. DepoTech will receive a share of the net sales and also payments totaling up to $19 million consisting of an initial cash payment and additional payments upon achievement of certain regulatory milestones. DepoCyt is responsible for manufacturing and ongoing clinical trials of the DepoCyt formulation and Pharmacia & Upjohn is responsible for submitting regulatory filings, labeling, packaging, distribution, marketing and

sales of DepoCyt outside the USA. On July 15, 1997, DepoTech announced the receipt of an initial $2 million payment from Pharmacia & Upjohn.

On November 19, 1997, DepoTech announced that it had received a notice of allowance from the USA Patent Office for a patent entitled, "Cyclodextrin Liposomes Encapsulating Pharmacologic Compounds and Methods for Their Use." The patent includes a novel method of prolonging drug release from liposomes and includes DepoFoam. The drug obtained orphan drug status for neoplastic meningitis in 1993.

HEMATOPOIETIC SUPPORT/BONE MARROW TRANSPLANTATION

Hematopoietic support is employed to mitigate the hematologic ravages of high-dose chemotherapy and also as a treatment approach for such CNS cancers as glioma and neuroblastoma. A small number of autotransplants, estimated at 250 annually, are performed worldwide in CNS cancer. Neuroblastoma cases account for over 50% of these. Published results regarding such transplants indicate that, in a relatively small numbers of patients with high-risk neuroblastoma, disease-free survival (DFS) rates range from 30% to 50%.

To establish the role of autotransplants in neuroblastoma, the Autologous Blood & Marrow Transplant Registry (ABMTR) plans to analyze its database of over 700 autologous BMT (autoBMT) procedures to provide a more precise estimate of outcome in groups defined by well-characterized prognostic factors. The study will also examine any association between patient-, disease- and treatment-related variables and outcome, and establish the efficacy of high-dose chemotherapy regimens and graft purging methodologies. The study also plans to define risk of late effects, such as second cancers, and assess functional status of long-term survivors of autotransplants. Also, in collaboration with the International Bone Marrow Transplant Registry (IBMTR), the study will compare the outcome of autoBMT and allogeneic BMT (alloBMT). The study, which is under the auspices of the IBMTR/ABMTR Pediatric Cancer Working Committee will be chaired by Naynesh R. Kamani, MD, Director, Pediatric Transplantation, at the University of Texas Health Science Center (San Antonio, TX).

Various parameters such as age, sex, nucleated cell dose, prior chemotherapy, prior CSI and bone marrow harvest site, may impact hematologic recovery after autoBMT. A study of 100 patients (median age=9 years) who underwent autoBMT for malignant brain tumors, evaluated two engraftment parameters, i.e. number of days post-autoBMT before an absolute neutrophil count (ANC) $\geq 0.5 \times 10^9$/l and a platelet count $\geq 50 \times 10^9$/l were achieved for the third consecutive day without transfusions. Increasing cell dose correlated significantly with a more prompt recovery of platelet counts and ANC. Previous chemotherapy significantly delayed both ANC and platelet engraftment. Platelet recovery and neutrophil engraftment in those also treated with CSI were delayed significantly with a median time to engraftment of 72 days and 23 days, respectively. This effect of CSI was independent of cell dose or prior chemotherapy. In 20 patients, marrow was harvested at least partially from the posterior iliac crests, which might have been exposed to significant doses of irradiation. Engraftment is significantly faster if bone marrow is harvested prior to any chemotherapy. Also, significant engraftment delay, particularly of the platelet lineage, occurs in patients treated with CSI before autoBMT. In this group of patients, bone marrow should not be harvested from the posterior iliac crests. Strategies that might enhance both neutrophil engraftment and platelet count recovery should be considered in patients with irradiation damage to a substantial proportion of the total hematopoietic tissue (Faulkner LB, etal, Bone Marrow Transplantation, 1996 Mar, 17(3):389-94).

High-dose busulfan (Myleran; Glaxo Wellcome) is used pre-operatively in children undergoing alloBMT or autoBMT for solid tumors, in particular brain tumors. In a phase II clinical trial conducted at Catholic University (Rome, Italy) "standard" dose, single-agent busulfan (200 mg/m^2) was administered orally over 2 days in 7 male and 3 female children between ages 2 and 18 years (median=7 years) with relapsed medulloblastoma/PNET and progressive disease. If MRIs showed no tumor progression at 4-5 weeks, busulfan (100 mg/m^2/day x 4 days) was re-administered followed by thiotepa (200 mg/m^2 IV x 3 days) followed by re-infusion of cryopreserved bone marrow or peripheral stem cells. There were 5 objective responses (4 PR and one minor response), disease stabilized in 4 and progressed in 1. Following BMT, further tumor reduction was noted in responders. The only side effect was Grade 2-4 neutropenia and thrombocytopenia (Tomesello A, etal, ASCO97, Abs. 1905:529).

It has been documented using gene-markers that infused neuroblastoma cells contribute to relapse following autologous stem cell transplantation (ASCT). Aliquots from peripheral blood stem cells (PBSCs), obtained after the third through fifth cycle of chemotherapy, were tumor-cell depleted using the CellPro (Bothell, WA) Ceprate LC Laboratory Cell Separation System to ensure tumor cell removal during selection for CD34+ hematopoietic progenitor cells. Of 31 PBSC aliquots processed, 9 (29%) pre-selected aliquots contained tumor cells. Of these, 6 (66.7%) showed no tumor cells post CD34+ selection and tumor cells were detectable in the remaining pre-and post CD34+ selection (Ross AA, etal, ASCO97, Abs. 353:101).

The Italian Bone Marrow Transplant Registry retrospectively studied 135 children (57 were in 1st CR, 11 in 2nd or subsequent CR, 42 in 1st PR, and 25 had more advanced disease) who underwent myeloablative therapy with BMT between 1984 and 1993 in nine Italian centers. Of these, 117 were treated with unpurged autoBMT, five with alloBMT and 13 with peripheral blood progenitor cells as rescue. Twelve children (9%) died of toxicity, 86 (73.5%) relapsed or progressed at median of 7 months (range=1 to

Exhibit 7
Standard and Emerging Treatment Approaches For Primary and Metastatic CNS Tumors by Histology Group in the USA

Surgery	Radiation	Chemotherapy
Malignant glioma		
Surgery is standard therapy for operable tumors	Conventional radiotherapy + thermoradiotherapy (combination of interstitial hyperthermia and brachytherapy with ^{192}Ir) (Stea B, etal, Int'l J Rad Onc Bio Phys 1994, 30:591-600); MST was 23.5 months (hyperthermia increased survival)	Busulfan is used as antineoplastic therapy in pediatric gliomas
	Intra-operative radiotherapy or 3-D conformal photon radiotherapy (Devita, Principles of Oncology 1997, 5th edition)	
	Dose-intensification of PCV with peripheral blood stem cell (PBSC) support in patients with newly diagnosed gliomas	
Sequential administration of an oral regimen, TPCH, a combination of 6-thioguanine, PCZ, CCNU and hydroxyurea (HU), before and after CCNU potentiates cytotoxicity and decreases drug resistance. From 1990 to 1996, 23 children [14 boys and 9 girls, aged 4-20 years, median =13 years)] with high grade astrocytomas with either AA (n=11) or GBM (n=12), were treated with adjuvant TPCH following surgery and radiation (see Exhibit 6)		
Astrocytoma-low grade (infiltrative)		
About 10%-35% are cured with surgery (Shaw EG, etal, J Neurosurgery 1989; 70: 853);5-year recurrence-free survival rate (SR) is 52% and 10-year SR is 23% after total or radical subtotal resection (Devita, *ibid*; Oncology, Nov 1997; 11(11A):239) (variability in SR reflects differences in age groups and the inclusion of patients with subtotal resection)	Radiotherapy involves limited radiation fields; standard dose is 54 Gy (1.8-2.0 Gy daily) with daily fractions of 1.8 to 2.0 Gy; increasing the radiation dose from 45 to 59 Gy had no effect on the 5-year survival rate (Van Glabbeken M, etal, ASCO95, Abs. 14;145)	
	Hyperfractionated irradiation and accelerated fractionation, as well as 3-D conformal photon radiotherapy, are currently being investigated as alternatives to conventional irradiation	
No randomized clinical trials have been performed comparing surgery alone to surgery plus radiation therapy		
5-year SR is 36%-55% for irradiated compared to 19%-32% for non-irradiated patients with subtotally resected tumors (McDonald DR, Semin Oncol 1994; 21:236-48); a retrospective study of cases from 1956-1990 showed that MST improved to 7.2-10 years with the advent of MRI and CT (Neurosurgery 1991;28:490)		
Newer modes of therapy include intra-operative radiotherapy		
	Chemotherapy, used in combination with radiation therapy, has not extended MST; in a randomized trial of radiotherapy with or without CCNU for incompletely resected low-grade gliomas, MST was the same in both arms (Eyre, etal, J Neurosurgery 1993;78:909)	
	A randomized RTOG trial comparing BCNU and hyperfractionated (72 Gy) with conventionally fractionated irradiation (60 Gy) was recently completed but results are not yet available. Clinical trials of accelerated fractionation involving conventional doses of radiation, administered twice to thrice daily, did not result in a survival benefit (Simpson WJ and Platts ME, Int'l J Rad Onc Bio Phys 1976;1:639)	
Astrocytoma, pilocytic (pediatric, non-infiltrative)		
5 to 10-year SR approaches 100% after complete or radical subtotal resection and/or radiation (Shaw EG, etal, J Neurosurgery 1989;70:853		
Oligodendroglioma or anaplastic oligodendroglioma		
Maximal feasible resection (gross total removal) is possible because 50% occur in frontal lobes	Radiation improves local control and survival (Bullard DE, etal, Cancer 1987; 60:2179-2188)	Anaplastic oligodendrogliomas are responsive to PCV and other agents (Cairncross J, etal, J Clin Oncol 1994; 12:2013-2021); PCV, is also being studied in conjunction with BMT

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Glioblastoma multiforme (GBM) or anaplastic astrocytomas (AA)		
Surgery is employed to biopsize the tumor, alleviate intracranial pressure symptoms and reduce need for corticosteroids; MST with surgery alone is 4 months	Demonstration of stepwise prolongation of survival with increasing dose (Walker, etal, Int'l J Rad Onc Bio Phys 1979;5:1725) has lead to treatment with a dose of 60 Gy in a single daily fraction of 1.8 to 2 Gy, 5x per week. The target volume is defined as a 2-3 cm margin of tissue surrounding the perimeter of the CT- or MRI-defined lesion. There were only 5% CR but 50% of those with AA and 25% with GBM responded significantly by the end of radiation therapy (Devita, *ibid*). MST in AA is 36 months and the 3-year SR is about 50%; MST in GBM is 10 months and the 3-year SR is 6% (Wong AJ, etal, Sem Onc 1994;21:139-48)	BCNU alone appears as effective as multi-agent chemotherapy (NCCN Proceedings, Oncology, Nov 1997; 11(11A):239)
		Immunotherapy using INF-β for recurrent malignant gliomas
		Gliadel has been approved for recurrent GBM
	Because radiotherapy is limited by the tumor's inherent radioresistance, use of radio-sensitizers or hyperthermia may improve outcome	
	BCNT is also being attempted (see text)	
	External partial brain irradiation (59.4 Gy) + 50 Gy by interstitial implantation resulted in SR of 87% at 1 year and 57% at 2 years compared to 40% and 12%, respectively, for a control group (Loeffler, etal, JNCI 1990; 82:1918)	
	Brachytherapy + external irradiation + chemotherapy is also being attempted	
	Phase II trial of BUdR (0.8 mg/m^2/d as a 96-hour infusion) during 6 weeks of irradiation, followed by a year of PCV	
Ependymoma		
Hemispheric ependymomas are often well circumscribed and are amenable to gross total resection which is highly effective		
Postoperative irradiation improves survival of patients with intracranial ependymomas; 5-year SR ranges from 40% to 87% (Biedler JL and Spengler BA, JNCI 1976;57:683-95)		
Anaplastic ependymoma		
Outcome is associated with extent of surgical resection; stereotactic surgery often used	54 Gy directed to the primary tumor + 36 Gy to the spinal axis; 5-year SR for irradiated patients is 33-80%	BCNU and DBD elicit a combined response of 75% and median time to progression of 13-16 months (Levin VA, etal, JNeurosurgery 1984;61: 1063). A 5-drug protocol (TPDCV) incorporating thioguanine, PCZ, DBD, CCNU and VCR) resulted in an 82% response rate and a median time to progression of 21 months (Devita *ibid*)
	High-dose hyperfractionated irradiation and precision-volume stereotactic radiosurgical "boosts" to residual tumor are being investigated (Oncology, Nov 1997; 11(11A):259)	
Medulloblastoma (MBL)		
Improvements in surgical techniques have increased tumor resectability and better peri-operatve management decreased incidence of severe complications	Whole craniospinal axis irradiation has improved effectiveness of radiation; however, late sequelae in long-term survivors of childhood MBL has prompted trials with lower doses which proved less effective; hyperfractionated radiation may be the treatment of choice in children <7 years-of-age	
Chemotherapy after surgery in infants results in a 3-year DFS of <25%; it is desirable that CSI be delayed as much as possible without jeopardizing its effectiveness or only be performed in relapsed cases; also, a lower dose of craniospinal radiation may be used prophylactically in responders		
Among 149 children 3-14 years-of-age with MBL, treated between 1975 and 1991 at King Faisal Specialist Hospital and Research Centre (Riyadh, Saudi Arabia) with surgery and CSI alone, the 8-year survival of T3 and T4 change stage patients (N=105) was 25%. In a pilot study, initiated in November 1994, outpatient chemotherapy was administered in children with high-risk posterior fossa MBL. After total or near total surgical resection and full course of CSI, patients were treated with weekly VCR (2 mg/m^2) x 5, followed by 12 monthly courses of VCR		

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(1.5 mg/m^2) and carboplatin (500 mg/m^2) alternated with VCR (1.5 mg/m^2) and CTX (750 mg/m^2). This regimen was feasible and associated with acceptable toxicity. An outpatient-based adjuvant chemotherapy, based on this regimen for children with MBL, is currently underway at Baylor College of Medicine and the Texas Children's Cancer Center (Houston, TX) (Mustafa MM, etal, ASCO97, Abs. 1447:405)		
Malignant menigioma		
MST of 6 patients treated with surgery was 7.2 months compared with 5.1 years for 12 patients who were treated with surgery plus radiotherapy. Recurrence rate for malignant meningioma was much higher among those exclusively treated with surgery (Chan and Thompson, J Neurosurgery 1984;60:521)		No defined role for chemotherapy exists for newly-diagnosed malignant meningiomas. Combinations of cytoxan, Adriamycin and VCR; DTIC and Adriamycin; and IFF and mesna, produced minimal response
Recurrent meningeal hemangiopericytoma (MHP)		
Aggressive surgical management is crucial in the treatment of recurrent MHP. Among 28 patients treated with surgery, with 50% having 2 or more procedures performed, median time to recurrence was 30 months (range=1 month to 9 years)	RT can have a palliative role; among 11 patients treated with radiation therapy, 2 achieved a PR, 9 remained stable with a median duration of 9 months, and 2 (both with spine metastases) progressed (Galanis, *ibid*)	Chemotherapy may also have a palliative role; doxorubicin-containing regimens administered in 7 patients resulted in 1 PR that lasted 8 months, while 3 remained stable for a median time of 6 months, and 3 progressed (Galanis E, etal, ASCO97, Abs. 1402:393)
Radiosurgery has a definite role for treatment of small or medium size CNS lesions, even in a previously irradiated field or after multiple resections. Of 10 patients with 20 metastatic CNS lesions (median size 42 mm) treated with radiosurgery, 3 (previously non-irradiated, lesion size < 25mm) achieved a CR; disease-free MST was 3 years. In 14 lesions (70%) PR was achieved with a median duration of 12 months while 3 lesions (15%) remained stable with a median duration of 6 months (Galanis, *ibid*)		
Neuroblastoma		
	Encouraging results have been reported with ^{131}I-MIBG in combination with chemotherapy	
	A regimen of melphalan (160-200 mg/m^2) + CTX (120 mg/kg) + total body irradiation (1200 cGy) was used in preparation for hematopoietic stem cell transplant (Park JR, etal, ASCO97, Abs. 1877:522)	
CNS germinoma		
	Radiation therapy is effictive in the treatment of intracranial germinoma and remains standard therapy	Carboplatin + V-16+ bleomycin is also effective as only treatment at initial diagnosis
	High-dose CTX + craniospinal irradiation (25.2-36 Gy) + a boost (45-54 Gy) at the site of recurrence is administered in relapsed patients; no failures occurred at a median follow-up after radiation therapy for an average of 24 months (range=8-39 months) (Merchant E, etal, ASCO97, Abs. 1409:395)	
Acoustic neuroma		
Surgery is effective in small tumors but in large tumors often results in deafness and facial neuropathy		
Single fraction radiosurgery of tumors ≤3 cm results in disease control but may cause facial and trigeminal neuropathy		
Fractionated stereotactic radiosurgery (2000 cGy in divided weekly dose of 400 or 500 cGy) controlled all 39 tumors (23 <3 cm and 16 >3 cm) treated (Lederman G, etal, ASCO97, Abs. 1439:403)		
Primary CNS lymphoma (PCNSL)		
Not amenable to surgical resection because of its diffuse nature	Primary treatment is whole brain radiotherapy; doses >5000 cGy are associated with better outcomes (Berry MP and Simpson WJ, Int'l J Rad Onc Bio Phys 1981; 7:55-59) but long-term survival with radiation therapy alone is poor (Murray K, etal, J Neurosurgery 1986;65:600-7) with recurrence rates of 92%	Substantial improvement in MST was noted in patients treated with chemotherapy (29 versus 16 months); glucocorticoids or dexamethasone achieve ORR in 33% of patients but most is short-lived; high dose MTX, ara-C, and cytoxan have also been tried (Fine HA and Mayer PJ, Ann Int Med 1993;119:1093-1104)
		In a prospective trial a combination of cytoxan and MTX, in conjunction with osmotic BBBD, followed by PCZ, in the initial treatment of PCNSL, resulted in an 81% RR; MST was in the order of 44.5 months (Neuwelt, etal, JCO 1991;91:580-90)

— *continued on next page*

	Preradiation chemotherapy extends survival 2 years (ASCO91;10:368)	
	Among 31 patients treated with a combination of IV and intraventricular MTX, followed by cranial irradiation and ara-C, MST was 42.5 months (DeAngelis, etal, JCO 1992;10:635-42)	
	Among 22 patients treated with three doses of MTX (3.5 mg/m^2) before radiation, CR occurred in 60% and PR in 31%; MST was 27 months (Gabbai, etal, J Neurosurgery 1989;70:190-4)	
Metastatic brain tumors		
Surgical resection of solitary brain metastasis in the absence of extracranial disease, results in enhanced survival; 50% of cases, however, are not surgical candidates because of inaccessible tumor, extensive systemic disease, or other factors (Loeffler J, etal, Oncology, Nov 1997; 11(11A):263)	Radiotherapy is the mainstay management approach; a total dose of 3000 cGy during a 2-week period is standard regimen (Borgett B, etal, Int'l J Rad Onc Bio Phys 1980;6:1-9)	Certain agents may reach the CNS through local breakdown in the BBB
	A phase III study is examining the impact of accelerated fractionated doses of radiotherapy (two treatments per day) on survival of patients with brain metastases	Metastases attributable to NHL, testicular and breast cancer, and sclc, are examples of tumors that can undergo complete radiographic remission with chemotherapy (Lester SG, etal, JCO 1984;2:1397-1403)
Emergency craniotomy may be performed to relieve intracranial pressure		Intra-arterial chemotherapy of cisplatin and etoposide is being attempted
In a randomized trial comparing whole brain radiation versus radiation plus surgery of solitary brain metastases, local control was superior in the surgery arm, 80% versus 48%, and survival was 40 weeks versus 15 weeks (Patchell, NEJM 1990;322:494-500)		
No ambulatory differences were observed in patients with single site spinal cord compression from metastatic cancer treated with radiation therapy alone (n=7) or "best" decompressive surgery plus postoperative radiation (n=7) (Payne R, etal, ASCO97, Abs. 275:79)		
Treatment with gamma-knife radiosurgery of 219 lesions in 100 evaluable patients with brain metastases at the University of California, San Francisco, from 1991 to 1994, indicated that a minimum prescribed dose ≥18 Gy yields excellent local control of brain metastases (Shiau CY, etal, Int'l J Rad Onc Bio Phys, 1997 Jan 15, 37(2):375-83)		
	Trials are ongoing with radioprotectors and/or radiosensitizers such as a cisplatin with radiotherapy	
	In a phase Ib/II trial, 10 daily IV injections of Gd-Tex are each followed by whole brain radiotherapy (Carde P, etal, ASCO97, Abs. 1388:389)	
	Among 39 patients treated with hematopoietic stem cell transplant using allogeneic bone marrow (alloBMT n=11), autologous autoBMT; (n=11) or PBSC (n=8), after chemotherapy and whole body irradiation, there were 16 CR and 10 PR for an ORR of 66.7% (Park JR, etal, ASCO97, Abs. 1877:522)	
Neoplastic meningitis		
	Cranial or craniospinal irradiation is being investigated (Blaney SM and Poplack DG, Investigational New Drugs, 1996, 14(1):69-85)	Frequent and repeated intrathecal administration, by intralumbar or intraventricular injection of high-dose MTX or ara-C, is standard treatment
		Very high-dose systemic chemotherapy is being attempted
		DepoCyt liposomal ara-C is in clinical trials
	Radiotherapy involving 2400 cGy administered as 8 fractions over 10-14 days and placement of an Ommaya reservoir in the right lateral ventricle to deliver MTX, or ara-C or thiotepa, is being evaluated	

68 months) and 80 of these subsequently died of progressive disease. Of the 43 (36.7%) children alive at the time of this review, 37 were in continuous remission at a median of 65 months (range=30 to 123 months) after BMT. Overall and DFS at 8 years was 28.5% and 26%, respectively. DFS was 34.6% for patients grafted in 1st CR, 23.6% in 1st PR, 36.4% in 2nd or subsequent CR, and 8% in those with advanced disease. It appears that early toxicity

of myeloablative therapy is manageable and treatment with bone marrow rescue may contribute to an improved long-term survival of children with advanced neuroblastoma, but a cure remains elusive (Garaventa A, etal, Bone Marrow Transplant, 1996 Jul 18:1 125-30 and Matthay KK, Bone Marrow Transplant, 1996 Dec 18 Suppl 3: S21-4).

A toxicity and efficacy study of a new conditioning regimen for BMT was performed on 27 children with advanced neuroblastoma. Patients were treated with teniposide [Vumon; Bristol-Myers Squibb (360 mg/m^2)] or VP-16 (500 mg/m^2), thiotepa (600-900 mg/m^2), and 1200 cGy fractionated total body irradiation (fTBI) followed by autologous marrow rescue (n=19) or alloBMT from HLA-identical siblings (n=8). The two patients treated with teniposide, 600 mg/m^2 thiotepa and fTBI, experienced minimal toxicity but relapsed 4 and 12 months post-autoBMT. The two patients treated with 750 mg/m^2 thiotepa, VP-16 and fTBI, tolerated the conditioning regimen well and were in remission 77 and 75 months post-BMT. Fatal toxicity was experienced by the first two allograft recipients who were administered thiotepa at the higher dose level. Subsequent allograft recipients were treated with 750 mg/m^2 thiotepa and autograft recipients with 900 mg/m^2 thiotepa. DFS was 21 to 77 months post-BMT in 8 (42%) of the 19 autoBMT patients. Nine autograft recipients relapsed at 2 to 37 months post-transplantation. One patient died of hepatic veno-occlusive disease 2 months after autoBMT, and one of pneumonia 6 months post-transplantation. Three allograft recipients relapsed at 6, 10 and 39 months post-transplant and three were alive and in remission 75, 53 and 27 months post-BMT. Overall, 11/27 (41%) patients were alive and in remission 21-77 months (median=47 months) following BMT. The tested conditioning regimen which consisted of 1200 cGy fTBI, and either 500 mg/m^2 VP-16 and 750 mg/m^2 thiotepa for allograft recipients or 900 mg/m^2 thiotepa for autograft recipients, was well tolerated and proved to be at least as effective as melphalan-containing regimens (Kamani N, etal, Bone Marrow Transplant 1996 Jun 17:6 911-6).

CURRENT TREATMENT BY TUMOR TYPE

Standard and investigative treatment for the various CNS cancers, described in FO pp 676-679, are summarized in Exhibit 7.

Primary Malignant CNS Cancer

The behavior of low-grade astrocytomas, a heterogeneous group of tumors, is variable making therapy and prognosis uncertain. Treatment of low-grade infiltrative astrocytomas is controversial and problematic because it seeks to prolong life without seriously compromising cognitive and emotional function. Although radiation therapy prolongs life, it does so at a cost, neurotoxicity.

Standard therapy of high-grade gliomas includes maximal resection followed by radiotherapy. Prospective clinical trials by the Brain Tumor Cooperative Group (BTCG) and the Scandinavian Glioblastoma Study Group confirmed the efficacy of radiotherapy in the treatment of malignant gliomas, both in terms of survival and quality of life. Addition of adjuvant chemotherapy has resulted in little improvement in survival but may have palliative effects.

Adding brachytherapy to external irradiation has gained favor in GBM. In a NCOG trial which evaluated brachytherapy as an adjunct to external irradiation and chemotherapy in GBM (Gutin, etal, Int'l J Rad Onc Bio Phys 1991;21:601-6), patients were treated with external irradiation (60 Gy) and oral hydroxyurea (300 mg/m^2) *qid*, followed by implants to deliver an additional minimum dose of 50-60 Gy, and were administered PVC every 6-8 weeks for 1 year. MST was 22 months which compared favorably to historical GBM controls. A phase III study conducted by the BTCG, randomly assigned patients with high grade gliomas to undergo BCNU plus external beam radiotherapy with or without brachytherapy (60 Gy). MST with brachytherapy was 16 months versus 13 months without (Green SB, etal, ASCO94, Abs. 486:174).

Intrestingly, post-operative infections may impart a survival advantage in high-grade astrocytomas (HGA) which are uniformly fatal with MST of approximately one year. Among 103 adults with newly diagnosed HGA enrolled in two phase II clinical trials who were treated with BCNU, CDDP and radiation, only 4 survived >4 years. Five of the 103 (5%) patients experienced post-operative bacterial infections at the site of their craniotomy requiring surgical debridement and antibiotics. MST of those who developed post-operative infection was 995 days compared to 386 days for those who did not. Furthermore, 2 of the 4 (50%) long-term survivors had infections following their initial tumor debulking surgery. Both of these patients, a 45 year-old with GBM and a 53 year-old with AA, were alive without evidence of recurrent disease at 5.8 and 4.2 years, respectively. Local infections following initial craniotomy may confer a long term survival advantage in patients with HGA who are also treated with radiation and aggressive chemotherapy (Borrello L, etal, ASCO97, Abs. 1416:397).

Surgery is standard therapy for ependymomas. Five-year survival of low-grade ependymomas is approximately 60%-80% and, for anaplastic ependymomas, it ranges between 10%-47% (JNCI 1976;57:683). When radiotherapy is used, most recommend inclusion of the entire craniospinal axis in the treatment of anaplastic ependymomas (Devita, *ibid*). However it is questionable if this leads to an improved survival because local recurrence is the primary failure. Regarding chemotherapy, several regimens including single and combination therapy have been used.

Pediatric Tumors

CNS cancer, although rare, is particularly devastating when it affects infants and children because many standard therapies result in deficits and adverse late effects. Also, malignant pediatric tumors of the CNS have a poor prognosis, with local failure rates as high as 50%. Based on

a health status questionnaire of 52 survivors of childhood CNS tumors, the group with the worse outcome were those with craniopharyngioma. Morbidity of children treated for craniopharyngioma is high and appears to be worse for those who experienced a relapse or who were older at diagnosis (Faestel PM and Foreman NK, ASCO97, Abs. 1427:400).

Between 1986 and 1990, POG conducted a study in which 198 children <3 years of age with malignant brain tumors were treated with prolonged postoperative chemotherapy in an effort to delay radiation and reduce long term neurotoxicity. Children <2 years of age were treated with 24 months of chemotherapy (see Exhibit 6) followed by radiation, and those between 2 and 3 years-of-age for 12 months. Five of 132 children <2 years of age at diagnosis developed second CNS malignancies but none occurred in the 66 patients who were 24 to 36 months of age at diagnosis. Additionally, 2 children developed myelodysplastic syndrome (MDS), 1 acute myelogenous leukemia (AML) and 2 solid tumors. Prolonged use of alkylating agents, VP-16 and radiation may be the cause for this high rate of 10 malignancies in children <3 years of age (Duffner P, etal, ASCO97, Abs. 1887:524).

Many reports on the outcome of children with CNS tumors include data from cases diagnosed prior to routine use of neuroimaging and treatment with chemotherapy. To assess the impact of these developments, the clinical course and outcome of children diagnosed with primary brain or spinal cord tumors from 1979 to 1995, before age 19, recorded from inpatient and clinic records at the University of Rochester, were reviewed (Exhibit 8). Of 52 (34%) children treated with radiotherapy alone, 9 (6%) with chemotherapy alone, 34 (22%) with both and 56 (37%) only with surgery, 112 (76%) survived at a median follow-up of 32 months (range 0 to 204 months). Short-term survival was very favorable for children with a broad spectrum of CNS tumors (Weinberg AS, etal, ASCO97, Abs. 1906:529).

Exhibit 8
Outcome of Children with CNS Tumors by Type

Types of Tumors	#	%	% Survivors (median follow-up in months)
Astrocytomas	61	40	
Low-grade	39		95 (25)
Intermediate-grade	16		81 (74)
High-grade	6		33 (23)
Medulloblastomas	20	13	60 (42)
Brainstem gliomas	15	10	40 (12)
Mixed gliomas	12	8	75 (56)
Gangliogliomas	8	5	100 (34)
Craniopharyngiomas	7	5	100 (28)
Ependymomas	6	4	100 (52)
Optic gliomas	6	4	83 (136)
Other tumors	17	11	65 (24)
Total	152	100	74 (32)

Metastatic Brain Tumors and Cancer Metastasized to the Brain

A metastatic brain tumor may appear anywhere in the brain or spine. For instance, meningeal hemangiopericytoma (MH), an uncommon meningeal tumor, exhibits a high propensity for both local recurrence and extraneural metastases. Among 34 consecutive patients [20 males and 14 females with a median age of 43 years (range=20 to 68 years)] treated between 1976 and 1996 at the Mayo Clinic (Rochester, MN), median time to first recurrence was 48 months (range=4 months to 16 years). Thirty-two patients (94%) recurred in the CNS and 14 (41%) extraneurally. Sites of extraneural disease were bones (86%), liver (43%), lungs (29%), and pleura, pancreas, breast, retroperitoneum and soft tissues (7%). MST from the time of first recurrence was 56 months and 5 patients remained disease-free for more than 10 years after first recurrence (Galanis E, etal, ASCO97, Abs. 1402:393).

In the case of cancers in other organs that have metastasized to the brain, if the primary cancer is under control, surgery or radiosurgery may be used to treat single brain tumors. Multiple tumors are also common. Radiation is the standard treatment for multiple tumors but chemotherapy may also be used, in addition to either surgery or radiation therapy. The goal of treatment for brain metastases is palliation of neurological systems and possibly prolongation of life. Radiotherapy is the primary treatment for brain metastases. Steroids are added to treat patients with and without symptoms. Brain tumors arising from metastatic melanoma have improved remission rates with accelerated fractionation in some groups of patients (Choi KN, etal, Cancer 1985;56:1-9). Radioprotectors such as amifostine (Ethyol; U.S. Bioscience) or radiosensitizers such as a CDDP with radiotherapy, are presently under evaluation.

MANAGEMENT OF TREATMENT-RELATED AND OTHER COMPLICATIONS

Complications associated with brain cancer include edema, seizures and various neurological deficits.

Hearing Loss

Sodium thiosulfate (STS) at high doses (16 gm/m^2 to 20 gm/m^2) may act as protectant against carboplatin-induced ototoxicity associated with the treatment of patients with malignant brain tumors. In a phase I clinical trial, 19 patients with malignant brain tumors who were treated with BBBD-carboplatin, were administered IV STS over 15 minutes, two hours after carboplatin. Because patients undergo monthly carboplatin plus BBBD treatment, STS was escalated on consecutive months from 4 gm/m^2 to 20 gm/m^2. There was a 23% incidence of ototoxi-

city in STS-treated patients, compared to 75% in controls. Average change in hearing for those treated with 16-20 gm/m^2 of STS for 3 months was less than 10 dB at 2000 Hz, in contrast to an average of 45 dB hearing loss in controls. Protection against ototoxic effects of carboplatin will increase applicability of BBBD chemotherapy (Neuwelt EA, etal, ASCO97, Abs. 1401:393).

Peritumoral Brain Edema

Shunts may be used temporarily, pre-operatively, to alleviate pressure from tumor-related edema or may have to remain in place over long periods of time. Shunts are catheters incorporating a unidirectional valve, that are inserted into a ventricle, and threaded under the scalp toward the neck into a body cavity such as the right atrium of the heart or, more commonly, the abdominal cavity, where fluid is drained and absorbed. Shunts are placed via a small hole in the skull.

Steroids, such as dexamethasone, prednisolone, and prednisone, control edema resulting from accumulation of fluids. Steroids are used temporarily following surgery or during radiation and for protracted periods for relief of symptoms. However, because of the potential side effects of these drugs, long-term use requires close monitoring.

Human corticotropin-releasing factor (hCRF) under development by Neurobiological Technologies (Richmond, CA) as Xerecept, is an endogenous peptide responsible for the secretion and synthesis of corticosteroids. In animal models of peritumoral brain edema, hCRF has significant anti-edematous action. This effect, which appears to be independent of release of adrenal steroids, appears mediated by a direct action on endothelial cells. A phase I study with hCRF administered by continuous infusion to 17 patients with brain metastasis, was recently concluded. The study was performed in two stages. In the feasibility part, patients were randomized to either 0.66 or 1 μg/kg/hr of hCRF or placebo, over 24 hours. The second part involved hCRF administration over 72 hours at escalating doses; hypotension was the DLT at 4 μg/kg/hr x 72 hours in 2/4 patients, while none of 5 patients treated at 2 μg/kg/hr developed DLT. Flushing and hot flashes were also observed. Improvement of neurological symptoms and/or exam were seen in 10 patients but, only small changes were detected by MRI. Improvement in symptoms did not correlate with changes in cortisol levels, and changes in cortisol levels were not correlated with changes in peritumoral edema (Villalona-Calero MA, etal, Annals of Oncology, Jan 1998, Vol. 9:1-7).

Seizures

It is common to use anticonvulsants (ACs) prophylactically in patients with brain tumors but their efficacy has been questioned. One study assessed reduction in seizure frequency and toxic effects in 100 newly-diagnosed brain tumor patients (61 men, median age=58 years) without prior history of seizures, randomly assigned to be treated with ACs (n=46) or not (n=54). Sixty patients had metastatic brain tumors, the most common attributed to lung cancer (n=32), breast cancer (n=9), and melanoma (n=4), and 40 had primary tumors, most commonly, GBM (n=28). Twenty-six of the 100 patients experienced seizures. Seizure-free survival did not differ between the two groups. Estimated seizure-free rate at 3 months after randomization was 87% in the group treated with ACs and 90% in the untreated group; at 6 months the rates were 69% and 80%, respectively. Seizure-free survival also did not differ between the two groups in an analysis stratified on the basis of tumor type (metastatic or primary). Generalized tonic-clonic seizures were no less common in the AC group (6/11, or 55%) than in the other group (7/15, or 47%). AC toxicities were minor, but were observed in (13/46, or 28%) of cases. This data does not support use of prophylactic ACs in patients with brain tumors (Weaver S, etal, ANA97, Abs. M151:68).

Recent data suggests that hepatic P450 enzyme-inducing anti-epileptic drugs can alter the pharmacology and toxicity of drugs such as paclitaxel and 9-AC. Also, in a retrospective review of phase II-III studies involving 1,200 patients with primary brain tumors treated with anticonvulsants from 1966-1996, doses of such chemotherapy agents as PCZ, 5-FU, and dibromodulcitol (DDB) that are metabolized in the liver and have some reported efficacy in high grade astrocytomas, were not modified but were similar to those used in systemic cancers where use of anticonvulsants is uncommon. Because anticonvulsants may alter the MTD of these agents, there is a need to address pharmacologic interactions prospectively in patients with brain tumors (Rich JN and Grossman SA, ASCO97, Abs. 1410:395).

MEETING COVERAGE

NEW THERAPEUTIC APPROACHES IN NEURO-ONCOLOGY

FROM THE 49TH ANNUAL MEETING OF THE AMERICAN ACADEMY OF NEUROLOGY BOSTON, MA, APRIL 12-19, 1997

GLIOMAS

Interferon β-1A

Many studies were undertaken over the past two decades, to evaluate the efficacy of biologic response modifiers, in general and interferons (IFN), in particular, in the treatment of malignant gliomas. IFN α and γ have shown only limited activity, however, a non-glycosylated recombinant INF β (Betaseron; Berlex) achieved overall response rates of 51% to 57%, although the duration of response was short. *In vitro* studies suggest that IFN β-1A (Avonex; Biogen), which is glycosylated like the natural human IFN β, may be more potent. IFN β-1A appears to be

active in high grade gliomas, although the therapeutic index appears to be low. In a phase I clinical trial, 16 patients with radiographically documented recurrent malignant gliomas (8 GBMs and 8 anaplastic astrocytomas) were treated thrice weekly with intramuscular injections of IFN β-lA. Five dose levels (2.0 to 10.0 mU/m^2) were used and patients were maintained on stable doses of steroids and underwent MRI scanning every six weeks.

All 16 enrollees were evaluable for toxicity and 13 for efficacy. Toxicity was seen in 14 patients (87.5%), with asymptomatic elevation in liver transaminase being the common adverse event. Other toxicities included anemia, neurotoxicity, thrombocytopenia, and leukopenia. Neurotoxicity was dose limiting at 8 mU/m^2, so the maximum tolerated dose (MDT) was 6 mU/m^2 administered thrice weekly. Five of 13 evaluable patients experienced partial radiographic responses. Median time to tumor progression was 36 days for the group, 89 days for responders, and 31 days for non-responders. Median survival was 86 days for all patients, 60 days for non-responders, and 188 days for responders. A phase II clinical trial at MDT is currently underway in recurrent gliomas (Fine AH, etal, AAN97, Abs. P01.003:A27).

Multimodality Regimens

A subset of patients with malignant glioma, > 70 years-of-age with a Karnofsky performance status (KPS) > 70, were assessed for response to surgery followed by radiotherapy at a low total dose in a small volume, and chemotherapy. In this study, 30 patients (18 with histologically proven glioblastoma, 7 with glioblastoma according to arteriographic criteria but without definitive histology, 3 with anaplastic oligoastrocytoma, 1 with anaplastic astrocytoma and 1 with anaplastic oligodendroglioma) underwent maximum possible resection. There were 5 complete surgical resections, 7 partial resections, 13 biopsies, and resection was not possible in 4 patients. Surgery was followed by a course of radiotherapy at a dose of 45 Gy in 25 fractions over five weeks with three or four orthogonal beams, with a 2.0 cm margin around the tumor bed. Twelve patients were treated with nitrosourea-based chemotherapy at a reduced dose (150 mg/m^2) every eight weeks, with a mean number of 2.5 of cycles delivered.

Among 27 evaluable cases, the overall median survival was 36 weeks and the median time to progression was 26 weeks. Three months or more after surgery and radiotherapy, there were five CR (18.5%), two PR (7.0%), and disease stabilized in 9 (33.3%). Radiotherapy was not completed in four patients because of neurological deterioration. The major prognostic factor for survival was the pre-radiotherapy KPS; a median survival of 40 weeks was noted in those with KPS >70 and 24 weeks in those with KPS <70 (Pierga J-Y, etal, AAN97, Abs. P01.004:A27).

High-dose Chemotherapy

High-dose chemotherapy (HDC) followed by stem cell support is well tolerated in patients with recurrent oligodendrogliomas even in those treated with prior myeloablative chemotherapy. HDC appears to be most effective when minimal disease is present and when treatment is administered immediately after induction chemotherapy, prior to further progression. In this study 5 patients with recurrent oligodenodroglioma who had responded or stabilized to a regimen of induction chemotherapy, underwent HDC. Treatment included surgery (gross total resection=3, subtotal resection=2), followed by radiation (n=3), or radiation plus combination chemotherapy (PCV) consisting of lomustine (110 mg/m^2) on day 1, procarbazine (60 mg/m^2) on days 8-21, and vincristine (1.4 mg/m^2) on days 8 and 29 (n=1) or radiation plus carmustine (n=1). Median time to first recurrence was 11 months. All patients underwent either biopsy or subtotal resection at recurrence.

Induction chemotherapy which consisted either of PCV (n=3) or carboplatin/etoposide (n=2), resulted in 2 CR, 2 PR, and disease stabilized in 1 patient. However, because of up to four months delays, caused by insurance coverage disputes regarding reimbursement of HDC, disease progressed in 4 before administartion of HDC. HDC regimens consisted of BCNU (450 mg/m^2) and etoposide (150 mg/m^2) twice daily, and thiotepa (600 mg/m^2) (n=4) or carboplatin (1500 mg/m^2), thiotepa (600 mg/m^2), and etoposide (1500 mg/m^2) over four days (n=1). Cell reconstitution was achieved with bone marrow support (n=1), stem cell support (n=2), and both (n=3). There were no deaths related to HDC and median duration of hospitalization was 23 days.

According to neurological tests one month after HDC, disease stabilized in 2 patients, new neurological signs appeared in another 2 and all signs were completely resolved in one. Median time to follow-up was 12 months (6-28 months range) after treatment. At the time of reporting these results, two patients had died of their disease, two were alive with stable radiographic abnormalities, and one, with no tumor detectable on MRI prior to starting HDC, was free of disease (Balmaceda C, etal, AAN97, Abs. V11.004:A18).

CNS LYMPHOMAS

Chemotherapy alone may result in a high response and survival rate when administered as initial treatment in elderly patients with primary central nervous system lymphoma (PCNSL), while also preserving cognitive function. There is, however, substantial myelosuppression. Radiotherapy combined with chemotherapy is presently the standard initial treatment for PCNSL, but radiotherapy causes delayed cognitive dysfunctions in elderly patients. Results from a pilot study with chemotherapy alone in individuals over 60 years-of-age were very encouraging, so the EORTC carried out a prospective seven-center study encompassing 23 elderly patients with PCNSL and a median KPS of 50. Induction therapy included methotrexate (1 gm/m^2) administered IV in three doses every 10 days, CCNU (40 mg/m^2 up to 100 mg/m^2) started on day one, procarbazine (60 mg/m^2) over

the first week, methylprednisolone (120 mg) every other day for 20 days, and intrathecal methotexate (15 mg) plus cytarabine (40 mg) every 4 days for two weeks. Chemotherapy was administered for six cycles or until signs of progression or intolerable toxicity.

Among the 21 patients evaluable for response, there were 16 (76%) CR and 3 (14%) PR, for an overall response of 90%. Disease progressed in two patients. The one-year survival rate was 70% and median survival had not been reached at the time of data presentation. Cognitive dysfunctions, evaluated by clinical exam, were present in 18 patients at diagnosis, with 13 improving with treatment, while 4 with progressive disease deteriorated, and 1 remained stable. Performance status improved in 14 patients and remained stable in 4. Grade 4 myelosuppression occurred in 4 patients (17%) and 2 (8%) experienced Grade 4 renal dysfunction (Khe H-X etal, AAN97, Abs. V11.001:A17).

Intravenous methotrexate (3 gm/m^2), every three to four weeks, is well tolerated and can induce CR both in hemispheric and vitreous PCNSL. To determine the feasibility of treating PCNSL with methotrexate, the charts of 10 patients with PCNSL (8 with B-cell lymphoma and 2 with atypical lymphoma), treated solely with IV methotrexate as primary therapy or after failure following irradiation, were reviewed. Methotrexate (3.0 to 3.5 gm/m^2 per cycle), was administered every three to four weeks in combination with leucovorin (25 mg) every six hours, starting 24 hours after chemotherapy, for a total of 16 doses. A median of 5 cycles was delivered. Overall clinical response rate was 100%, with 5 CR and 5 PR. Radiographic response parallelled the clinical improvement in 4 patients, occurred earlier than clinical response in 4 partients, and, in 2, there was a dramatic clinical response within 2 days after chemotherapy, but the MRI still showed residual lesions. Three patients have since died. The remaining were still alive at the time of presentation, having survived from 5 to 37+ months, all free of disease. As toxicity is moderate, methotrexate may be administered in a maintenance mode in an effort to delay or avoid radiation therapy. Further studies are needed to determine the lowest and optimal dose of IV methotrexate for PCNSL, the best schedule of administration, and the duration of therapy (Balmaceda C, etal, AAN97, Abs. V11.002:A17).

PARANEOPLASTIC NEUROLOGICAL SYNDROMES

Paraneoplastic neurological syndromes (PNS) are disorders pathologically related to cancer but not ascribable to nervous system metastases or other non-metastatic cancer-related mechanisms, such as coagulopathy and vascular disorders, infections, metabolic and nutritional deficits, or toxic effects of treatment. They may affect any part of the nervous system, with one cell type (Parkinje cells in paraneoplastic cerebellar degeneration) predominantly involved, or, in other cases, any or all neurons of the central or peripheral nervous system may be affected (paraneoplastic encephalomyelitis in lung, breast, gynecological, or gastrointestinal cancers). In more than two thirds of patients, symptoms of PNS develop before a cancer is diagnosed. Suspicion of PNS, therefore, may lead to early diagnosis of tumors and correct identification of PNS avoids unnecessary diagnostic testing (Poaner JB, AAN97, Educational Syllabus Vol 7, 1997; 218: Pg 218-19).

Paraneoplastic opsoclonus/encephalopathy

Paraneoplastic opsoclonus/encephalopathy syndrome attributable to inappropriate antidiuretic hormone secretion (SIADH) may respond to early high-dose IV methylprednisolone (IVMP) and IV gammaglobulin (IVGG) in patients with occult small-cell lung cancer (sclc). Adult opsoclonus is an uncommon, disabling neurological sign which might herald the discovery of an incipient malignancy. Though the tumor may sometimes be cured, oscillopsia is usually resistant to most therapies. In a previously healthy 65-year old woman, examination uncovered oscillopsia, dizziness, ataxia, seizures, and SIADH. Chest x-ray revealed a 4 mm rounded area in the upper left lobe. Because of the seriousness of the syndrome, effective treatment became imperative to relieve the disabling symptoms, including potentially lethal acute hyponatremia, before tissue biopsies could be safely and reliably performed. Within a few hours of combined treatment with IVMP and IVIG, opsoclonus, ataxia, and SIADH completely resolved. Lung biopsy, done three weeks after onset of immunotherapy and while opsoclonus had disappeared, was diagnostic for sclc. Surgery was followed by chemotherapy and slow tapering of IVMP and IVIG. The patient completely recovered and is currently asymptomatic (Werner J, etal, AAN97, Abs. P01.007:A28).

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) had a remarkable preliminary response to interleukin-2 (IL-2) in a woman with small cleaved cell lymphoma in remission following autoBMT. Current therapies for PML, including IFN a and cytosine arabinoside, have been largely ineffective. This patient developed progressive hemiparesis, aphasia, and typical features of PML on serial MRI scans. PML was proven by *in situ* hybridization for JC papovavirus and typical neuropathologic features in brain biopsy tissue taken three months after symptom onset. IL-2 (105 units/m^2) was administered IV five times daily with no other therapy. Objective improvement in speech and motor function was seen within two weeks of initiation of treatment. When IL-2 therapy was stopped after four weeks, clinical worsening occurred one week later, which responded dramatically to re-initiation of IL-2. An objective MRI response was noted after four more weeks of IL-2, with near complete resolution after five months of continuous therapy. Near complete clinical and MRI responses persisted nine months after stopping IL-2. Because of the untreatable, life-threatening nature of PML, these findings are very promising, particularly in light of the increase in incidence of PML in AIDS and BMT patients (Jaeckle KA, AAN97, Abs. P01.002:A26).

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