Pathology:
Differentiation and Prognosis in Medulloblastoma

Peter Burger, M. D.
Duke University

Historically, little attention was given to the differentiation potential of the medulloblastoma, particularly in regard to prognosis and therapy. Although neuroblastic or neuronal features were recognized in some neoplasms, little practical importance was attached to these features in a neoplasm generally felt to be undifferentiated. Recently, however, there has been considerable attention to the histologic heterogeneity of the medulloblastoma, due in part to the suggestion that the medulloblastoma may be considered as only one of a family of primitive neuroectodermal tumors that may, but do not always, express differentiation into neuronal, astrocytic, ependyma, oligodendroglia, and/or neuroblastic lines (1). The frequency with which such differentiation occurs, and the extent of association with a specific biologic behavior, however, remains controversial.

The most easily recognized differentiation in medulloblastomas is that along neuroblastic lines. This alteration is readily appreciated in standard histologic sections in the form of neuroblastic rosettes. Although the precise incidence of this feature is not well recorded, our own experience utilizing material from the European cooperative pediatric study (SIOP) would suggest that 40% or more of medulloblastomas have light microscopic evidence of neuroblastic differentiation (2). Another finding of neuronal/neuroblastic differentiation is that of large mature ganglion cells. Although it can be difficult in some cases to differentiate such neoplastic cells from normal entrapped neurons, it is clear that a small percentage of medulloblastomas have such cells.

It was hoped that the application of immunohistochemistry using antibodies in neurofilament proteins would assist in the characterization of neuroblastic differentiation. The results have been disappointing because of the poor reactivity of such antibodies in paraffin-embedded tissue and the paucity of this antigen in the poorly differentiated neuroblasts of most neuroblastic medulloblastomas (2). Current efforts are underway to identify fixatives for which neurofilament staining is better suited. In addition, there are also studies in progress to identify and localize other "neuron-specific" antigens within these neoplasms. Electron microscopy has been helpful in characterizing neuroblastic features in some lesions, however, there are considerable sampling problems in infiltrating lesions of the brain and it is difficult to identify neurons as entrapped versus neoplastic (3). It will be therefore be difficult to utilize electron microscopy as a means of defining neuronal differentiation and/or its incidence.

Glial differentiation in the medulloblastoma has been considerably more difficult to define than has neuroblastic differentiation. This is a consequence of the difficulty of distinguishing between the fibrillary processes produced by glial differentiation and that produced by reactive gliosis, entrapped normal brain, and some neuroblastic neoplasms (4). In addition, it is apparent that astrocytic differentiation, if it takes place, is generally a rather focal and poorly developed phenomenon without the overt differentiation into mature astrocytes. The use of immunohistochemistry has been helpful and defines in some cases unequivocal staining of neoplastic cells with positively staining short bipolar processes (2,5). It has been our observation that this differentiation rarely extends to the form of

extremely well differentiated astrocytes. The incidence of astrocytic differentiation in our experience has been approximately 5-10% (2). There are, however, a number of cases in which the interpretation of immunohistochemistry is problematic (4). In such cases, there are positively staining cells which could represent neoplastic cells but which cannot be equivocally so identified. Thus the incidence of astrocytic differentiation remains to be defined.

Oligodendroglial differentiation has been identified in a number of medulloblastomas in the form of cells with the classic "fried egg" appearance (1). However, the exact nature of such cells is not clear and the frequent association with overt neuroblastic findings elsewhere in the lesions suggests that some of these "oligodendroglial" foci could be neuronal rather than oligodendroglial. Ependymal differentiation has been noted in some medulloblastomas in the form of the classic perivascular pseudorosettes. In this setting, however, it can be difficult to differentiate between medulloblastoma and an anaplastic ependymoma. In addition, a perivascular type of rosette is a common feature in neuroblastic lesions and some of the reported examples of ependymal differentiation in medulloblastomas may be neuroblastic.

The influence of differentiation on survival is a critical issue which at this point remains controversial. In one study, patients with medulloblastomas that were "differentiated" had shorter survival times than those with tumors that were non-differentiated (6). However, the number of patients was limited and the precise descriptions of the various lesions were not given and not illustrated. Thus it was not clear how many of the differentiated lesions were neuroblastic, astrocytic, etc. A more recent study analyzed a number of histologic factors and concluded, on the contrary, that patients with the differentiated lesions do better (7). In this report, the "differentiated" lesions were combined also and the figures were not given as to what percent were neuroblastic, glial, or both.

Thus, conflicting views have been expressed as to the prognostic influence of differentiation. Since it seems possible that certain lesions, such as neuroblastic lesions, might respond differently to radiotherapy than the glial and undifferentiated lesions, it would be desirable to analyze cases in regard to the exact type of differentiation and not combine all lesions with differentiation in the statistical analysis. Additional features must also be considered, since two studies have indicated that some of the traditional features used to grade brain tumors are also influential prognostic factors. Thus, in one study it became apparent that lesions with little cytoplasm, many mitoses, and necrosis behaved more aggressively than other lesions (8). Another investigator has indicated that the presence of necrosis was prognostically significant (7).

The medulloblastoma is clearly a heterogenous lesion which has been difficult to characterize by traditional methods, even with the application of immunohistochemistry which often is assumed to identify "specific" cell types. It is hoped that better immunologic markers for embryonic development will help elucidate the origin of these lesions and provide a better means for prognostication.

Cytogenetic and molecular biologic studies of medulloblastoma are at this point few, however they may provide potential methods to improve the above traditional approaches to classification. In light of the observation that the amplification of the n-myc oncogene associated with a higher stage and poor

prognosis in some peripheral neuroblastomas (9), the presence of the expression of this oncogene is of special interest in the neuroblastic medulloblastoma. Studies of oncogene amplification in the medulloblastoma are presently in progress. Cytogenetic studies have only been done in a few cases, and it is too soon to be certain as to the prognostic significance, if any, for the cytologic abnormalities detected (10).

REFERENCES

1. Rorke LB : The cerebellar medulloblastoma and its relationship to primitive neuroectodermal tumor. J Neuropathol Exp Neurol 42:1-15, 1983.

2. Burger PC, Grahmann FC, Bliestle A, et al. : Differentiation in the medulloblastoma: A histological and immunohistological study. Acta Neuropathol (in press).

3. Matakas F, Cervos-Navarro J : The ultrastructure of medulloblastomas. Acta Neuropathol 16:271-284, 1970.

4. Coffin CM, Mukai N, Dehner LP : Glial differentiation in medulloblastomas. Histogenetic insight, glial reaction, or invasion of brain. Am J Surg Pathol 7:555-565, 1983.

5. Kumanishi T, Washiyama K, Watabe K, Sekiguchi K : Glial fibrillary acidic protein in medulloblastomas. Acta Neuropathol 67:1-5, 1985.

6. Packer RJ, Sulton LN, Rorke LB, et al. : Prognostic importance of cellular differentiation in medulloblastoma of childhood. J Neurosurg 61:291-301, 1984.

7. Caputy AJ, McCullough DC, Manz HJ, Patterson K, Hammock MK : A review of the factors influencing the prognosis of medulloblastoma. The importance of cell differentiation. J Neurosurg 66:80-87, 1987.

8. Kopelson G, Linggood RM, Kleinman GM : Medulloblastoma - the identification of prognostic subgroup and implications for multimodality management. Cancer 51:312-319, 1983.

9. Seeger RC, Brodeur GM, Sather H, et al. : Association of multiple copies of the N-myc oncogene with rapid progression of neuroblastomas. New Eng J Med 313:1111-1116, 1985.

10. Bigner SH, Mark J, Friedman HS, Biegel JA, Bigner DD : Structural chromosomal abnormalities in human medulloblastoma. (Submitted.)

Surgery for Medulloblastoma: Techniques and Problems

Fred Epstein, M. D.
New York University Medical Center

This presentation will be directed toward the preoperative assessment, intraoperative technique and postoperative management of children with medulloblastoma.

PREOPERATIVE ASSESSMENT AND TREATMENT

Computerized axial tomography is usually diagnostic of a medulloblastoma, revealing a patchy density prior to contrast infusion and homogenous enhancement following contrast. In the presence of this "classical" picture, the diagnosis is virtually certain and angiography does not contribute to either the diagnosis or the operative management. The MRI scan may offer additional information vis-a-vis the relationship between the tumor and the floor of the fourth ventricle and may occasionally suggest infiltration of the latter. While this may be helpful, there is no experience to suggest that this is an indispensable adjunct.

The routine placement of a "preoperative" shunt should be relegated to neurosurgical history. There are many reasons not to do a shunt, not the least of which is the potential for tumor dissemination, upward herniation and hemorrhage into the tumor. It is the very rare patient who is not stabilized by corticosteroids and even in these circumstances a temporary ventricular drain may be preferable to the insertion of a shunt.

SURGERY - ITS GOAL

There is only one surgical goal and that is gross total removal of the tumor. This is technically feasible in 95% of patients and is only occasionally not possible when fragments of the tumor infiltrate the floor of the fourth ventricle.

It is essential to emphasize that there is no justification to abandon resection of a medulloblastoma because of its size or for concern on the part of the surgeon that "deep" cerebellar structures are being violated. The cerebellar peduncles as well as the dentate nuclei are displaced away from the tumor and, as long as the surgical resection is confined to the bulk of the tumor, it is feasible to extract it in its entirety. Normal white matter can then be visualized surrounding the residual tumor cavity.

An issue that is sometimes raised is whether or not a radical removal of the posterior fossa tumor could be carried out if the preoperative CT scan or MRI scan suggests that there are already disseminated metastases. From my point of view, there is no alternative to removing the bulk of the neoplasm, and the surgeon must not be dissuaded from this endeavor in the presence of disseminated disease.

POSTOPERATIVE MANAGEMENT

Many patients who have had large medulloblastomas removed develop transient supranuclear palsies manifested by slurred speech, facial diplegia, as well as ocular motor imbalance. This characteristically occurs 48 to 72 hours after surgery and disappears within a few days to several weeks. It is my impression that it is due to some sort of delayed vascular spasm, although cerebellar edema extending through the brachium pontis into the brain stem is also a possible cause. In any event, it is important that this very common syndrome not be regarded as a brain stem injury and that it not impede an "extent of disease workup" and subsequent therapy.

Approximately 40-50% of children who have had advanced hydrocephalus require a shunt sometime during the postoperative period. It is my perspective that if a significant pseudomeningocele develops within two or three days of surgery, it is better to put in the shunt early rather than delaying it for a few days, which will delay the postoperative treatment plan. The issue as to whether or not a Millipore filter should be inserted is not resolved. While systemic metastases have been documented with and without shunts, there is a strong suggestion that the placement of a shunt makes it somewhat more likely. While the filter offers the theoretic advantage of removing the tumor cells, it poses additional problems. A filter is prone to blockage by virtue of its physical properties. In addition, it is only the occasional tumor that metastasizes through the shunt and it is my personal bias that these are highly malignant and disseminated tumors which are biologically aggressive, with a poor prognosis with or without a conventional shunt. In addition, I believe that the extent of disease work up or the surgical anatomy will place these patients in the "poor risk" category and that subsequent chemotherapy will diminish the small possibility of systemic metastasis.

The most common site of recurrent medulloblastoma is in the posterior fossa. Obviously, these tumors are biologically aggressive and the prognosis is poor with or without adjunctive therapy. Nevertheless, it is my perspective that a large recurrent tumor should be removed prior to utilizing adjunctive therapy.

It must be emphasized that children who have been treated for medulloblastoma with neuraxis radiation with or without chemotherapy may have demonstrable lesions in the brain which are not necessarily recurrent tumor. We have cared for two patients (ages 11 and 14 years) who have had recurrent frontal hemorrhages which were initially interpreted as bleeding into a tumor nodule, but were later recognized to be hemorrhage secondary to radiation-induced vasculitis. Following surgery, they had a full recovery and have not had evidence of tumor for 1 and 6 years, respectively.

A third child was noted to have a small enhancing lesion at the parieto-occipital junction on a routine follow-up CT scan. This was interpreted as probable tumor, but because of its atypical appearance, a craniotomy was carried out. At that procedure, the lesion could not be localized either visually or with intraoperative ultrasound and a postoperative CT scan disclosed that it was gone. Angiography subsequently disclosed a few absent vessels and it appeared that this case demonstrated a radiation-induced infarction secondary to alterations of the local vascular supply. Although describing these cases is anecdotal, it emphasizes the very important point that it cannot be taken for granted that abnormalities demonstrated on postoperative imaging studies might

not be due to recurrent tumor.

It is becoming apparent that patients remain at risk for tumor recurrence for many years, if not permanently. We have encountered recurrent neoplasms as well as radiation-induced malignant gliomas in the region of previous resections ten to fifteen years after the original surgery. Three low grade astrocytomas, one sarcoma and two glioblastomas have been observed and might be associated with the radiation. Therefore it is essential to reoperate on late "recurrences" as they are likely to be treatment-induced neoplasms that are histologically different from the primary tumor.

REFERENCES

1. Al Mefty O, Jinkins JR, el Senoussi M, el Shaker M, Fox JL : Medulloblastomas: a review of modern management with a report on 75 cases. Surg Neurol Dec 24(6):606-624, 1985.

2. McLaurin RL : Disadvantages of the preoperative shunt in posterior fossa tumors. Clin Neurosurg 30:278-285, 1983.

3. Albright AL : The value of precraniotomy shunts in children with posterior fossa tumors. Clin Neurosurg 30:278-285, 1983.

4. Hoffman HJ, Hendrick EB, Humphreys RP : Management of medulloblastoma in childhood. Clin Neurosurg 30:226-245, 1983.

5. Papo I, Caruselli G, Luongo A : External ventricular drainage in the management of posterior fossa tumors in children and adolescents. Neurosurg Jan 10(1):13-15, 1982.

6. McComb JG, Davis RL, Isaacs H Jr : Extraneural metastatic medulloblastoma during childhood. Neurosurg Nov 9(5):548-551, 1981.

7. Kleinman GM, Hochberg FJ, Richardson EP Jr : Systemic metastases from medulloblastoma: a report of two cases and review of the literature. Cancer Nov 15:48(10):2296-2309, 1981.

8. Raimondi AJ, Tomita T : Hydrocephalus and infratentorial tumors. Incidence, clinical picture and treatment. J Neurosurg Aug 55(2):174-182, 1981.

9. Berry MP, Jenkins RD, Keen CW, Nair BD, Simpson WJ : Radiation treatment for medulloblastoma. A 21-year review. J Neurosurg Jul 55(1):43-51, 1981.

10. Raimondi AJ, Tomita T : Medulloblastoma in childhood: comparative results of partial and total resection. Childs Brain 5(3):310-328, 1979.

RADIATION THERAPY FOR MEDULLOBLASTOMA

Larry E. Kun, M.D.
St. Jude Children's Research Hospital
Memphis, Tennessee

Medulloblastoma has been the sentinal tumor establishing principles of radiation therapy for central nervous system neoplasms. Harvey Cushing's initial review of his experience with this tumor documented both the limitations of surgery and the early promise of radiation therapy. Local infiltration and recurrence following surgery, apparent radioresponsiveness, and the tendency for subarachnoid dissemination identified the challenge of providing potentially curative post-operative irradiation.

Early reports of survival after radiation therapy confirmed the efficacy of this modality. Five-year survival in 20-25% of children even in the 1940's contrasted with Cushing's series noting only one 3-year survivor in 61 cases. The frequency of neuraxis dissemination was documented in McFarland's 1969 review, fully one third of reported cases seeding the CSF pathways. With recognized limitations assessing intracranial disease status in earlier series, clinicians appreciated the high proportion of metastasis largely along the spinal axis. Irradiation evolved from posterior fossa to posterior fossa plus spine and, ultimately, to craniospinal volumes. Bloom's report in 1969 established the baseline experience with orthovoltage techniques for craniospinal irradiation, confirming 32% 5-year survival and 25% 10-year survival.

Recent reports of modern surgery and radiation therapy document 5-year survival rates approaching 50-60%. Identification of prognostic factors including host factors, tumor extent, and perhaps tumor biology, highlight current clinical investigations of both more aggressive combined-modality therapy and less aggressive neuraxis therapy for "high risk" and "low risk" groups, respectively. Added therapeutic endeavors are now being investigated to improve survival in the former group; control rates approaching 70% with conventional irradiation have led to attempts to limit late toxicities by reducing the intensity of therapy in the latter group.

ADVANCES IN MODERN MANAGEMENT

Improvements in neuroradiology, surgical techniques and intent, and radiation therapy have combined to achieve overall 50-60% or higher long-term, disease-free survival in medulloblastoma. Beyond the appreciation of local tumor extent possible with CT and MR scanning, recent reports document clinically occult, macroscopic neuraxis dissemination in 20-30% of cases at presentation. Identifying this subset allows better definition of the "low risk" group (i.e. those with apparently "total" surgical resection and negative neuraxis staging) and, importantly, the opportunity to more aggressively address those cases with minimal established CSF seeding.

Current radiation therapy techniques include fastidious attention to patient positioning and immobilization, permitting precise field alignment in what is easily identified as the most technically demanding tool in the radiation oncologist's armamentarium: craniospinal irradiation. Customized casts or molds for patient positioning permit a degree of accuracy otherwise not readily achieved. Linear accelerators provide a well-defined, easily collimated supervoltage photon beam which can be precisely aligned to homogeneously irradiate the entire subarachnoid space. Individually designed blocks limit irradiation to the desired target volume, substantially reducing irradiation of adjacent normal structures. Through education and participation in multi-institutional clinical trials, expertise in the practical aspects of craniospinal irradiation have improved technical accuracy quite impressively. Experience in the Pediatric Oncology Group (POG) has shown an increase in the rate of "technically appropriate" radiation therapy on a national scale from only 50-60% in 1979 to over 90% in 1986. Population-based data continue to show a statistical benefit for those patients treated in major university centers, yet emphasizing the desirability of centralizing the demanding treatment for this tumor.

RADIATION THERAPY PARAMETERS : VOLUME

The necessity to irradiate the entire subarachnoid space has been repeatedly confirmed. Despite a single, unique report of 10-year survival in 11/18 cases McFarland treated to the posterior fossa and spine, the broader experience indicates serial improvement in disease control with full neuraxis irradiation. Landberg reported 5% in survival following local posterior fossa irradiation, 25% with treatment to the posterior fossa and spine, and 53% after craniospinal irradiation.

Two recent reports highlight the importance of irradiation volume. A multi-institutional French trial using an effective chemotherapy regimen ("8-in-1") prior to posterior fossa plus spinal irradiation reports subarachnoid failure, primarily in the supratentorial region, in 11/15 cases. (Brunat-Mentigny) A smaller Italian series shows similar results with attempts to limit the volume of irradiation to the posterior fossa alone in conjunction with MOPP chemotherapy.(Lombardi)

A reported "pattern of failure" indicating a high proportion of subfrontal recurrences attests to the necessity to encompass all aspects of the subarachnoid space, technically accurate series rarely identifying disease recurrence at this site.(Jereb)

RADIATION THERAPY PARAMETERS : DOSE

Both primary tumor control in the posterior fossa and survival relate strongly to the dose delivered to the posterior fossa. Doses of $\geq$50 Gy (5000 rad) have been associated with improved local tumor control, with reports of 40-50% disease control after 45-50 Gy in contrast to 75-80% following 50-55 Gy. The sharp dose-response curve at 50 Gy has been confirmed in several modern series. Survival parallels the improvement in control at the primary tumor site, with reports of 5-year disease-free survival in excess of 50-70% only in cases receiving $\geq$50 Gy to the posterior fossa.

Doses to the full cranium and spine are less well established. Large series quoting survival rates above 50% have predominately followed 35-45 Gy (3500-4500 rad) to the cranium and 30-40 Gy (3000-4000 rad) to the spine. Recent reports from Northwestern University and Harvard's Joint Center for Radiation Therapy suggest equal survival rates after only 25-26 Gy to the cranium and spine, primarily in the "low risk" group of children with limited primary tumor extent and "total" surgical resection.(Tomita, Brand, Hughes) Both POG and the Children's Cancer Study Group (CCSG) are prospectively addressing this question, randomizing a selected "low risk" group with T_{1-2} tumor extent by Chang's staging system, gross surgical removal, and negative neuraxis staging to "conventional doses" (35-36 Gy) or "reduced doses" (24-25 Gy) to the cranium and spine, maintaining 54 Gy to the posterior fossa. A definitive answer to this dose related issue is important both to confirm the efficacy of a lower dose in controlling microscopic neuraxis disease and to assess the presumed reduction in late effects associated with lower irradiation levels.

RADIATION THERAPY PARAMETERS : TIME-DOSE RELATIONSHIP

Fractionated irradiation requires continuous, uninterrupted daily treatment to optimize control rates in most human tumor systems. Specific data from Berry's report confirms this principle in medulloblastoma: survival in children treated without interruption was 62% compared to only 37% in those treated with interruptions of 3-5 days or more. It is important to continuously irradiate the posterior fossa site, even in those cases requiring temporary cessation of neuraxis therapy due to transient hematosuppression. Current studies addressing combinations of chemotherapy and irradiation must account for this potential to maximize the efficacy of irradiation following initial drug therapy.

PATTERNS OF FAILURE

Analysis of failure patterns following craniospinal irradiation show the majority of recurrences to be at the posterior fossa primary site. A literature review of 343 patients completing CSI reveals recurrences in 53%, with follow-up ranging from 2 to >10 years. As clinically assessed, failure in the posterior fossa with or without concurrent meningeal metastasis was reported in 19-58% of cases. In sum, 36% of the treated patients have shown primary recurrences. Of all patients with tumor recurrence, the posterior fossa was involved in 68%. Spread through the subarachnoid space as a site of first disease recurrence was noted in 9% of all cases. Recent studies document a frequency of cephalad extension equal to that of caudal extension to the spinal canal. Isolated meningeal metastasis accounted for 17% of recurrences; in total, subarachnoid disease was identifiable at the time of first failure in 37% of instances. Extraneural metastasis as a first site of failure was noted in 8% of the reviewed cases, accounting for 14% of all recurrences.(Kun)

NORMAL TISSUE REACTIONS

Acute Effects

Normal tissue reactions during the course of radiation therapy are anticipated, varying in degree with individual host factors. Leukopenia and/or thrombocytopenia are noted during the third week of fractionated irradiation, infrequently requiring interruption in craniospinal irradiation. The neutrophil and platelet count return to normal levels within 4-8 weeks, with prolonged T-cell lymphopenia documented several months-to-years after irradiation. Transient, mild anemia is apparent at the end of a 6-8 week course of therapy.

Epithelial reactions are generally moderate, with alopecia and erythema or hyperpigmentation beginning during the third week of radiation therapy. There is normally complete return of scalp hair beginning 3-4 months post-irradiation; incomplete return may be noted, particularly along the tangentially irradiated vortex or posterior occipital regions. Epithelial reactions of both the skin and esophagus may be enhanced in patients receiving prior chemotherapy (e.g. cisplatin, methotrexate).

Fatigue and appetite suppression frequently accompany radiation therapy, although nausea and vomiting is generally limited to the adolescent age group. Minor reduction in daily fraction size may eliminate this problem.

Subacute Effects

Central nervous system symptoms and signs occurring within the first two months post-irradiation have been well documented as a "subacute phenomenon." Transient fatigue, low grade fever or enhancement of local neurologic signs (e.g. ataxia, cranial nerve findings) occur in approximately 40% of patients. Neurologic signs have been attributed to a delayed effect on the oligodendrocytes, experimentally attributed to a transient demyelinization which has been rarely documented on CT or MR studies.

Late Effects

Appropriate concern has recently been focused on late neurologic and neuropsychologic effects of radiation therapy. Neurologic sequelae, identified as cerebral necrosis or myelopathy occurring 6-24 months after irradiation, have rarely been documented in the setting of properly fractionated, technically accurate irradiation for medulloblastoma. The identified dose-response relationship of improved disease control at 50-54 Gy to the posterior fossa approaches the tolerance level of normal brain tissue. An incidence of post-irradiation necrosis approaching 5% has been estimated for dose levels approximating 55-60 Gy. Although combinations of irradiation and chemotherapy have been shown to reduce normal tissue tolerance in many organ systems, clinical reports describing enhanced irradiation reactions are limited to interactions of methotrexate and radiation therapy. Laboratory models have identified cisplatin and nitrosoureas as potential radiosensitizers in specific tissue settings, leading one to note appropriate caution in documenting both subacute and late effects of current treatment regimens testing various combinations of cytotoxic chemotherapy and full dose irradiation.

Neuropsychologic changes have been increasingly described in longterm survivors of medulloblastoma. Hirsch' report comparing children with cerebellar astrocytoma with a relatively matched set of medulloblastoma patients highlights concern regarding intellectual function as a consequence of therapeutic irradiation. Several selected series indicate average full scale IQ levels 10-20 points below the normal population. There have been relatively few prospective studies, available reports suggesting subnormal values at the time of diagnosis while confirming a statistically significant decline over a 2-5 year period after treatment. Subsequent improvement in intellectual studies has been described following added time and/or directed educational activities. Specific neuropsychologic changes have been identified, in particular changes in memory and selective attending. Overall changes in intellectual capacity and specific deficits in memory function correlate primarily with children below 4-8 years of age at diagnosis. Prospective, comparative studies are yet required to quantify the treatment-related changes in this critical parameter. Concerns regarding more severe neuropsychologic changes in children treated with combined chemotherapy and irradiation will also need to be addressed in the context of current therapeutic trials.

Growth changes have been documented following craniospinal irradiation. Direct effects upon growing bone have been well described, with particular reference to decrease in ultimate vertebral height following irradiation in children prior to puberty. Change in height may also reflect a secondary effect from direct hypothalamic-pituitary irradiation. Reduction in growth hormone secretion has been documented in 30-50% of children followed beyond 1 year post-irradiation. Decreased secretion of TSH and gonadotropins has been uncommonly documented; post-irradiation diabetes insipidus has not been observed. Serial endocrine studies to detect hypofunction are indicated, prompt initiation of replacement therapy limiting the degree of height reduction seen in this population.

An enlarging population of children "cured" will provide increasing information regarding the frequency of secondary tumors. Benign osteochondromas are relatively common following radiation therapy. Although thyroid carcinoma has been reported in up to 7-10% of children receiving relatively low doses to the thyroid gland in early childhood, case reports of thyroid cancer following successful treatment for medulloblastoma have been anecdotal to date. Controlled series in other childhood tumors appear to show a reduction in post-irradiation malignant neoplasms from as high as 10-14% following orthovoltage treatment to approximately 1% following supervoltage therapy. Secondary sarcomas, meningiomas or interaxial CNS tumors have been rarely reported. The increased frequency of second malignant tumors following combined therapy with alkylating agents and radiation therapy in other tumor systems heightens the necessity to closely monitor the medulloblastoma population following more aggressive multimodality regimens.

Selected References

Berry, MP, Jenkin, RDT, Keen, CW, Nair, BD, Simpson, WJ: Radiation treatment for medulloblastoma: A 21-year review. J Neurosurg 55:43-51, 1981.

Bloom, HJG: Medulloblastoma in children: Incresing survival rates and further prospects. Int J Radiat Oncol Biol Phys 8:2023-2027, 1982.

Bloom, HJG: Intracranial tumors: Response and resistance to therapeutic endeavors, 1970-1980. Int J Radiat Oncol Biol Phys 8:1083-1113, 1982.

Bloom, HJG, Wallace, ENK, Henk, JM: The treatment and prognosis of medulloblastoma in children: A study of 82 verified cases. Am J Roentgenol 105:43-62, 1969.

Brunat-Mentigny, M, Bernard, JL, Tron, P, Bachelot, C, Carton, M, Philip, T, Dutou, L, Alphonsi, SM, Raybaud, C, Lapras, C: Treatment of medulloblastomas with surgery-chemotherapy and radiation therapy limited to the posterior fossa and the spinal cord. Presented at SIOP XVIII Annual Meeting, Beograd, Yugoslavia, 1986. (abstr)

Chang, CH, Housepian, EM, Herbert, C: An operative staging system and a megavoltage radiotherapeutic technic for cerebellar medulloblastomas. Radiology 93:1351-1359, 1969.

Danoff BF, Cowchock, FS, Marquette, C, Mulgrew, L, Kramer, S: Assessment of the long-term effects of primary radiation therapy for brain tumors in children. Cancer 49:1580-1586, 1982.

Deutsch, M: The impact of myelography on the treatment results for medulloblastoma. Int J Radiat Oncol Biol Phys 10:999-1003, 1984.

Deutsch, M, Reigel, DH: Myelography and cytology in the treatment of medulloblastoma. Int J Radiat Oncol Biol Phys 7:721-725, 1981.

Duffner, PK, Cohen, ME, Anderson, SW, Voorhess, ML, MacGillivray, MH, Panahon, A, Brecher, ML: Long-term effects of treatment on endocrine function in children with brain tumors. Ann Neurol 14:528-532, 1983.

Duffner, PK, Cohen, ME, Thomas, P: Late effects of treatment on the intelligence of children with posterior fossa tumors. Cancer 51:233-237, 1983

Harisiadis, L, Chang, CH: Medulloblastoma in children: A correlation between staging and results of treatment. Int J Radiat Oncol Biol 2:833-841, 1977.

Hirsch, JF, Renier, D, Czernichow, P, Benveniste, L, Pierre-Kahn, A: Medulloblstoma in childhood. Survival and functional results. Acta Neurochir 48:1-15, 1979.

Hughes, EN, Winston, K, Cassady, JR, Tarbell, NJ: Medulloblastoma: Results of surgery and radical radiation therapy at the JCRT 1968-1984. Presented at SIOP XVIII Annual Meeting, Beograd, Yugoslavia, 1986. (abstr)

Jereb, B, Reid, A, Ahuja, RK: Patterns of failure in patients with medulloblastoma. Cancer 50:2941-2947, 1982.

Kopelson, G, Linggood, RM, Kleinman, GM: Medulloblastoma: The identification of prognostic subgroups and implications for multimodality management. Cancer 51:312-319, 1983.

Kun, LE, D'Souza, B, Tefft, M: The value of surveillance testing in childhood brain tumors. Cancer 56:1818-1823, 1985.

Kun, LE, Mulhern, RK: Neuropsychologic function in children with brain tumors: II. Serial studies of intellect and time after treatment. Am J Clin Oncol (CCT) 6:651-656, 1983.

Kun, LE, Mulhern, RK, Crisco, JJ: Quality of life in children treated for brain tumors: intellectual, emotional, and academic function. J Neurosurg 58:1-6, 1983

Landberg, TG, Lindgren, ML, Cavallin-Stahl, EK, Svahn-Tapper, GO, Sundbarg, G, Garwicz, S, Lagergren, JA, Gunnesson, VL, Brun, AE, Cronqvist, SE: Improvements in the radiotherapy of medulloblastoma, 1946-1975. Cancer 45:670-678, 1980.

Lombardi, F, Gasparini, M, Fossati-Bellani, F, Rottoli, L: Failure of postoperative MOPP + posterior fossa radiotherapy in radically resected medulloblastoma. Presented at SIOP XVIII Annual Meeting, Beograd, Yugoslavia, 1986. (abstr)

Mulhern, RK, Kun, LE: Neuropsychologic function in children with brain tumors: III. Interval changes in the six months following treatment. Med P Oncol 13:318-324, 1985.

Park, TS, Hoffman, HJ, Hendrick, EB, Humphreys, RP, Becker, LE: Medulloblastoma: clinical presentation and management. Experience at the Hospital for Sick Children, Toronto, 1950-1980. J Neurosurg 58:543-552, 1983.

Sheline, GE, Wara, WM, Smith, V: Therapeutic irradiation and brain injury. Int J Radiat Oncol Biol Phys 6:1215-1228, 1980.

Silverman, CL, Simpson, JR: Cerebellar medulloblastoma: The importance of posterior fossa dose to survival and patterns of failure. Int J Radiat Oncol Biol Phys 8:1869-1876, 1982.

Tomita, T, McLone, DG: Medulloblastoma in childhood: results of radical resection and low-dose neuraxis radiation therapy. J Neurosurg 64:238-242, 1986.

CHEMOTHERAPY OF RECURRENT MEDULLOBLASTOMA

Michael S.B. Edwards, M. D.
University of California, San Francisco

Modern techniques of surgery, irradiation, and chemotherapy for the initial treatment of medulloblastoma have improved survival, however, approximately 60% of patients will fail initial treatment within 10 years. At recurrence, chemotherapy has been shown to be of benefit in producing palliation. Although many chemotherapeutic agents can induce substantial rates of remission for varying periods of time, they have not cured patients harboring recurrent medulloblastoma.

The following is a tabulation of single- and multi-drug chemotherapeutic regimens that have shown activity against recurrent medulloblastoma. Medulloblastoma shows sensitivity to many agents albeit the duration of responses may be short. Multi-drug regimens have been more effective than single-drug regimens and the sequential use of different non-cross resistant regimens may produce quality survival for years in 25% to 50% of patients.

The following tables and references summarize those drug treatments that have produced responses in CNS, CSF, and bony/extraneural disease. The interested physician should review the original publications carefully to determine the dosage schedule, route of administration, response criteria and, most importantly, the toxicity. When chemotherapy is no longer effective or toxicity unacceptable, the use of CNS axis re-irradiation should be considered. Such therapy has produced extended quality survival for 12 to 18 months.

Hopefully, new chemotherapeutic agents and techniques will continue to improve the outlook for children with recurrent medulloblastoma.

SINGLE AGENT CHEMOTHERAPY for RECURRENT MEDULLOBLASTOMA

REFERENCE	SINGLE AGENT	RESPONSE	COMMENT
Gyepes et.al. (1)	Actinomycin D	0/1	Extraneural disease
Benjamin et.al. (2)	Adriamycin	0/6	CNS disease
Eduards et.al. (3)•	Ara C	1/12	CSF disease
Schold et.al. (4)	AZQ	1/2	CNS disease
CCSG:2/9/87 (5)	AZQ	1PR+4SD/19	CNS disease
Walker et.al. (6)	BCNU	0/2	CNS disease
Feuer et.al. (7)•	BCNU	1/3	CNS disease
Shapiro et.al. (8)	BCNU	1/3	CNS disease
Walker et.al. (9)	Carboplatin	5/7	CNS disease
Allen et.al. (71)	Carboplatin	3CR+3PR/14	CNS disease
Feuer et.al. (10)•	CCNU	0/1	CNS disease
Rosenblum et.al. (11)	CCNU	0/1	CNS disease
Shapiro et.al. (12)	CCNU	0/1	CNS disease
Ward HWC. (13)	CCNU	2/2	CNS disease
Garrett et.al. (14)	CCNU	2/2	CNS disease
Wilson et.al. (15)•	CCNU	1/1	CNS disease
Ward HWC. (16)	CCNU	7/7	CNS disease
Walker et.al. (17)	Cisplatinum	5/7	CNS disease
Bertolone et.al. (18)	Cisplatinum	2/10	CNS disease
Feun et.al. (19)	Cisplatinum	1/1	Bony metastases
Sexauer et.al. (20)	Cisplatinum	4/10	CNS disease
Stolzenberg et.al. (21)	Cyclophosphamide	1/1	Bony Metasteses
Allen et.al. (22)	Cyclophosphamide	7/7	3 CNS, 3 Bone marrow,
Wienblatt et.al. (23)	Dianhydrogalactitol	0/4	CNS disease
Levin et.al. (24)•	Dibromodulcitol	2R + 8SD/20	CNS disease
UCSF 1987 •	Dibromodulcitol	4R + 11SD/29	CNS disease
Finkelstein et.al. (25)	DTIC	0/1	CNS disease
Norrell et.al. (26)	Methotrexate (IT)	1/1	CNS disease
Newton et.al. (27)	Methotrexate (IT)	9/11	CNS disease
Wilson et.al. (28)	Methotrexate (IT)	2/2	CNS disease
Sayers MP. (29)	Methotrexate (IT)	19/? No denominator	No patient details
Shapiro et.al. (12)	Methotrexate (IT)	0/1	CNS disease
Norrell et.al. (30)	Methotrexate (IT)	0/2	CNS disease
Eduards et.al. (3)•	Methotrxate et.al.	2/5	CSF disease
Rosen et.al. (31)	Methotrexate (IV)	5/7	CNS disease
Djerassi et.al. (32)	Methotrexate (IV)	0/1	CNS disease
Abelson et.al. (33)	Methotrexate (IV)	1/1	CSF & Bony disease
Mooney et.al. (34)	Methotrexate (IV)	0/5	CNS disease
Borowska et.al. (35)	Nitrogen Mustard	0/1	Bony Metastases
Hancock et.al. (36)	PCNU	0/4	CNS disease
Kumar et.al. (37)•	Procarbazine	3/4	1CNS and 2 CSF disease
Eduards et.al. (3)•	Thio-Tepa (IT)	1/2	CSF disease
Berry et.al. (38)	Uracil Mustard	1/1	CNS disease
Drachman et.al. (39)	Vincristine	1/1	Bony metastases
Haddy et.al. (40)	Vincristine	0/1	CNS disease
Lassman et.al. (41)	Vincristine	1/1	CNS disease
Lassman et.al. (42)	Vincristine	2/2	CNS disease
Lampkin et.al. (43)	Vincristine	1/1	Spinal Cord lesion
Smart et.al. (44)	Vincristine	1/2	CNS disease
Lassman et.al. (45)	Vincristine	2/2	Bony metasteses
Brutschin et.al. (46)	Vincristine	0/1	Bony metastases
Afra D. (47)	Vincristine	1/1	CNS disease

REFERENCE	SINGLE AGENT	RESPONSE	COMMENT
Rosenstock et.al. (48)	Vincristine	3/4	CNS disease
Christ et.al. (49)	Vincristine	1/1	CNS disease
Lassman LP. (50)	Vincristine	2/2	Bony metastases
Skylansky et.al (51)	VP 16	1/1	CNS disease

• = UCSF STUDY

R = response
PR = partial response
SD = stable disease

MULTI-AGENT CHEMOTHERAPY for RECURRENT MEDULLOBLASTOMA

REFERENCE	MULTI AGENT	RESPONSE	COMMENT
Gutin et.al. (52)•	Procarbazine, CCNU, Vincristine (PCV)	5/5	CNS disease
Crafts et.al. (53)•	Procarbazine, CCNU, Vincristine (PCV)	10/16	CNS disease
Levin et.al. (54)•	Procarbazine, CCNU, Vincristine (PCV)	7/19	CNS disease
Duffner et.al. (55)	Vincristine, Methotrexate, BCNU	4/4	CNS disease
Seiler RW. (56)	VM26, CCNU, Prednisone	2/3	CNS disease
Cangir et.al. (57)	Nitrogen Mustard, Vincristine, Prednisone, Procarbazine (MOPP)	8/10	CNS disease
Cangir et.al. (58)	MOPP	4/9	CNS disease
CCSG/ Pendergrass et.al. (73)	VCR, CCNU, PCB, Ara C, Methylpred., Hydroxyurea, cis-Plat., DTIC "8 in 1"	4CR + 14PR/30	CNS disease
Cangir et.al. (58)	OPP	3/12	CNS disease
Lewis et.al. (59)	Vincristine, BCNU	1/1	Bony metastases
Kessler et.al. (60)	Vincristine, CCNU	1/1	Bony metastases
Shapiro et.al. (12)	BCNU, Methotrexate	2/2	CNS disease
Hagler et.al. (61)	Vincristine, Cyclophosphamide	1/1	Bony metastases
Banna et.al. (62)	Vincristine, Cyclophosphamide	1/2	Bony metastases
Debnam et.al. (63)	Vincristine, Cyclophosphamide	0/2	Bony metastases
Parkinson et.al. (64)	Vincristine, Cyclophosphamide	0/1	Bony metastases
Christ et.al. (49)	Vincristine, Cyclophosphamide	2/3	Bony metastases
Freidman et.al. (65)	Vincristine, Cyclophosphamide	4/4	Bony metastases
Freidman et.al. (65)	Vincristine, Cyclophosphamide	4/8	CNS disease
Nathanson et.al. (66)	VCR, Actinomycin, Cyclophosphamide	2/2	Bony metastases
Ettinger et.al. (67)	Cyclophosphamide, VCR, Prednisone, Procarbazine	1/3	CNS disease
UCSF-84ZZ •	6-TG, CCNU, DBD, PCB, VCR	1CR + 2SD/8	CNS disease
Chamberlin et.al. (70)•	Cytoxan, Adriamycin, Vincristine	6CR + 2PR/8	Bony/Extraneural disease
Spencer et.al. (69)	MOPP	1CR/1	Bony disease
Spencer et.al. (69)	HD-MTX	1PR/2	Bony disease
Spencer et.al. (69)	Cytoxan, Adriamycin, Procarbazine	1PR/1	Bony disease
Spencer et.al. (69)	CCNU, VCR, (IT) MTX	1PR/1	Bony disease
Lowery et.al. (74)	Vincristine, Adriamycin, Cytoxan (CAV)	2PR/4	Bony disease
Thomas et.al. (72)	VCR, BCNU, Dexamethasone, (IV) MTX: (5 pts. also had XRT)	6CR + 2PR/8	CNS disease
Van Eys et.al. (68)	Cis-platinum	1/2	CNS disease
Van Eys et.al. (68)	HD-MTX, PCNU	0/1	CNS disease

• = UCSF STUDY

6-TG = 6-Thioguanine; DBD = Dibromodulcitol; PCB = Procarbazine
VCR = Vincristine; MTX = Methotrexate;

CR = Complete Response
PR = Partial Response
SD = Stable Disease

REFERENCES

1. Gyepes MT, D'Angio. Extracranial metastases from CNS tumors in children and adolescents. Radiology 87:55-63,1966.

2. Benjamin RS, Wiernik PH, Bachur NR. Adriamycin chemotherapy-efficacy, saftey, and pharmacologic basis of an intermittent single high-dose schedule. Cancer 33:19-27,1974.

3. Edwards MS, Levin VA, Seager ML, Wilson CB. Intrathecal chemotherapy for leptomeningeal dissemination of medulloblastoma. Child's Brain 8:444-451,1981.

4. Schold SC, Freidman HS, Bjornson TD, Falletta JM. Treatment of patients with recurrent primary brain tumors with AZQ. Neurology 34:615-619, 1984.

5. Aziridinylbenzoquinone (AZQ) for solid tumors and lymphomas. CCG-085, L. Ettinger (Chmn.) in preparation 2/9/87.

6. Walker MD, Hurwitz BS. BCNU (1,3-Bis(2-chloroethyl)-1-Nitrosourea); (NSC-409962) in the treatment of malignant brain tumor - A preliminary report. Cancer Chemother Rep 54:263-271, 1970.

7. Fewer D, Wilson CB, Boldrey EB, Enot Kj, Powell MP. Chemotherapy of brain tumors - clinical experience with carmustine and vincristine. JAMA 222:549-552, 1972.

8. Shapiro WR. Chemotherapy of primary malignant brain tumors. Cancer in Children 35:965-972, 1975.

9. Walker RW, Allen JC, Bacha D, Tan C. Treatment of recurrent primary brain tumors of childhood with carboplatin. Ann Neurology 18:406, 1985.(ABST: 14th Annual Child Neurology Meeting, Memphis,Tenn. Oct.10-12,1985).

10. Fewer D, Wilson CB, Boldrey EB, Enot JK. Phase II study of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) in the treatment of brain tumors. Cancer Chemother Rep 56:421-427, 1972.

11. Rosenblum ML, Reynolds AF, Smith KA, Rumack BH, Walker MD. Chloroethyl-cyclohexyl-nitrosourea (CCNU) in the treatment of malignant brain tumors. J Neurosurg 39:306-314, 1973.

12. Shapiro WR, Cheromme NL, Posner JB. Necrotizing encephalopathy following intraventricular instillation of methotrexate. Arch Neurol 29:96-102, 1973.

13. Ward HWC. CCNU in the treatment of recurrent medulloblastoma. Br Med J 1:642, 1974.

14. Garrett MJ, Hughs HJ, Ryall RDH. CCNU in brain tumors. Clin Radiol 25:183-184, 1974.

15. Wilson CB, Gutin PH, Boldrey EB, Crafts D, Levin VA, Enot KJ. Single-agent chemotherapy of brain tumors. Arch Neurol 33:739-744, 1976.

16. Ward HWC. Central nervous system tumors of childhood treated with CCNU, vincristine and radiation. Med Ped Oncol 4:315-320, 1978.

17. Walker RW, Allen JC. Treatment of recurrent primary intracranial childhood tumors with cis-diamminedichloroplatinum. Ann Neurology 14:371-372, 1983.

18. Bertolone SJ, Baum E, Krivit W, Hammond D. Phase II trial of cisplatinum diamino dichloride (CPDD) in recurrent childhood brain tumors: A CCSG trial. Proc Am Assoc Cancer Res 2:72, 1983.

19. Feun LG, Savaraha N, Ozarda AT. Cisplatin in medulloblastoma with extracranial metastases: A case report. Cancer Treat Rep 68:1307-1308, 1984.

20. Sexauer CL, Kahn A, Burger PC, Krischer JP, Van Eys J, Vats T, Ragab AH. Cis-Platinum in recurrent pediatric brain tumors: A POG Phase II study. Cancer 56:1497-1501, 1985.

21. Stolzenberg J, Fisher JJ, Kligerman MM. Extradural metastasis in medulloblastoma 10 years after treatment. AM J Roent 108:71-74, 1970.

22. Allen JC, Helson L. High-dose cyclophosphamide chemotherapy for recurrent CNS tumors in children. J Neurosurg 55:749-756, 1981.

23. Weinblatt ME, Ortega JA, Huggins GR, Siegel SE. Dianhydrogalactitol in the treatment of children with primary brain tumors. Cancer Treat Rep 65:923-924, 1981.

24. Levin VA, Edwards MSB, Gutin PH, Vestnys P, Fulton D, Seager M, Wilson CB. Phase II evaluation of dibromodulcitol in the treatment of recurrent medulloblastoma, ependymoma, and malignant astrocytoma. J Neurosurg 61:1063-1068, 1984.

25. Finklestein JZ, Albo V, Ertel I, Hammond D. 5-(3,3-Dimethyl-1-triazano)imidazole-4-carboxamide in the treatment of solid tumors in children. Cancer Chemother Rep 59:351-357, 1975.

26. Norell H, Wilson C. Brain tumor chemotherapy with methotrexate given intrathecally. JAMA 201:93-95, 1967.

27. Newton WA, Sayers JP, Samuels LD. Intrathecal methotrexate for brain tumors in children. Cancer Chemother Rep 52:257-261, 1968.

28. Wilson CB, Norell HA. Brain tumor chemotherapy with intrathecal methotrexate. Cancer 23:1038-1045, 1969.

29. Sayers MP. Surgery and chemotherapy of brain tumors in children. Progr Exp Tumor Res 17:414-442, Karger, Basel, 1972.

30. Norell H, Wilson CB, Slagel DE, Clark DB. Leukoencephalopathy following the administration of methotrexate in to cerebrospinal fluid in the treatment of primary brain tumors. Cancer 33:923-932, 1974.

31. Rosen G, Ghavimi F, Nirenberg A, Mosende C, Mehta BM. High-dose methotrexate with citrovorum factor rescue for the treatment of central nervous system tumors in children. Cancer Treat Rep 61:681-690, 1977.

32. Djerassi I, Kim JS, Shulman K. High-dose methotrexate-citrovorum factor rescue in the management of brain tumors. Cancer Treat Rep 61:691-694, 1977.

33. Abelson HT, Kufe DW, Skarin AT, Major P, Ensminger W, Beardsley GP, Canellos GP. Treatment of central nervous system tumors with methotrexate. Cancer Treat Rep (Supp 1) 65:137-140, 1981.

34. Mooney C, Souhami R, Pritchard J. Recurrent menulloblastoma - lack of response to high-dose methotrexate. Cancer Chemother Pharmacol 10:135-136, 1983.

35. Borowska LF, Junkowska A, Kamraj-Mazurkiewica K. Cerebellar medulloblastoma metastases to skeletal system in children. Pol Prezegl Radiol 33:429-434, 1969.

36. Hancock C, Allen J, Tan CTC. Phase II trial of PCNU in children with recurrent brain tumors and Hodgkin's disease. Cancer Treat Rep 68:441-442, 1984.

37. Kumar ARV, Renaudin J, Wilson CB, Boldrey EB, Enot KJ, Levin VA. Procarbazine hydrochloride in the treatment of brain tumors. J Neurosurg 40:365-371, 1974.

38. Berry DH, Fernbach DJ, Sutow WW, Vietti TJ. Uracil mustard (NSC 34462) therapy in uncommon malignant neoplasms in children. Cancer Chemother Rep 52:441-443, 1968.

39. Drachman DA, Winter TS, Karon M. Medulloblastoma with extracranial metastases. Arch Neurology 9:518-530, 1983.

40. Haddy TB, Ferbach DJ, Watkins WL, Sullivan MP, Windmiller W. Vincristine in uncommon malignant disease in children. Cancer Chemother Rep 41:41-45, 1964.

41. Lassman LP, Pearce GW, Gang J. Sensitivity of intracranial gliomas to vincristine sulfate. Lancet 1:296-298, 1965.

42. Lassman LP, Pearce GW, Gang J. Effect of vincristine sulfate on the intracranial gliomata of childhood. Brit J Surg 53:774-777, 1966.

43. Lampkin BC, Maurer AM, McBride BH. Response of medulloblastoma to vincristine sulfate: A case report. Ped 39:761-763, 1967.

44. Smart CR, Ottoman RE, Rochlin DB, Hornes J, Silva AR, Goepfert H. Clinical experience with vincristine in tumors of the central nervous system and other malignant diseases. Cancer Chemother Rep 52:733-741. 1968.

45. Lassman LP, Pearce GW, Banna M, Jones RD. Vincristine sulphate in the treatment of skeletal metastases from cerebellar medulloblastoma. J. Neurosurg 30:42-49, 1969.

46. Brutschin P, Culver GJ. Extracranial metastases from medulloblastomas. Neuroradiol 107:359-361, 1973.

47. Afra D. Vincristine therapy in malignant glioma recurrences. Neurochirurgia 16:189-198, 1973.

48. Rosenstock JG, Evans AE, Schut L. Response to vincristine of recurrent brain tumors in children. J. Neurosurg 45:135-140, 1976.

49. Christ WM, Ragab AH, Vietti TJ, Ducos R, Chu J-Y. Chemotherapy of childhood medulloblastoma. Am J Dis Child 13:639-642, 1976. 50. Lassman LP. Diagnosis and management of skeletal metastases from cerebellar medulloblastoma. Child's Brain 2:38-45, 1976.

51. Skylansky BD, Mann-Kaplan RS, Reynolds BF, Rosenblum ML, Walker MD. 4' -Demethyl-epipodophyllotoxin- -D-thenylidene-glucoside (PTG) in the treatment of malignant intracranial neoplasms. Cancer 33:460-467, 1974.

52. Gutin PH, Wilson CB, Kumar ARV, Boldrey EB, Levin V, Powell M, Enot KJ. Phase II study of procarbazine, CCNU, vincristine combination chemotherapy in the treatment of malignant brain tumors. Cancer 35:1398-1404, 1975.

53. Crafts DC, Levin VA, Edwards MS, Fischer TL, Wilson CB. Chemotherapy of recurrent medulloblastoma with combined procarbazine, CCNU, vincristine. J Neurosurg 49:589-592, 1978.

54. Levin VA, Vestnys PS, Edwards MS, Wara WM, Fulton D, Barger G, Seager M, Wilson CB. Improvement in survival produced by sequential therapies in the treatment of recurrent medulloblastoma. Cancer 51:1364-1370, 1983.

55. Duffner PK, Cohen ME, Thomas PRM, Sinks LF, Freeman AI. Combination chemotherapy in recurrent medulloblastoma. Cancer 43:41-45, 1979.

56. Seiler RW. Combination chemotherapy with VM26 and CCNU in primary malignant brain tumors of children. Helv Paediat Acta 35:51-56, 1980.

57. Cangir A, Van Eyes J, Berry DH, Hvizdala E, Morgan SK. Combination chemotherapy with MOPP in children with recurrent brain tumors. Med Ped Oncol 4:253-261, 1978.

58. Cangir A, Ragab AH, Steubner P, Land VJ, Berry DH, Kirschner JP. Combination chemotherapy with vincristine, procarbazine, prednisone with or without nitrogen mustard (MOOP vs OPP) in children with recurrent brain tumors. Med Ped Oncol 12:1-3, 1984.

59. Lewis MD, Nunes LB, Powell DE, Schrader BI. Extra-axial spread of medulloblastoma. Cnacer 71:1287-1297, 1973.

60. Kessler LA, Dugan P, Concannon JP. Systemic metastases of medulloblastoma promoted by shunting. Surg Neurol 3:147-152, 1975.

61. Hagler S, Currimbhay ZE, Tinsley M. Cerebellar medulloblastoma. Chemotherapeutic remission with cyclophosphamide, and methotrexate. Cancer 21:912-919, 1968.

62. Banna M, Lassman LP, Pearce GW. Radiological study of skeletal metastases from cerebellar medulloblastoma. Br J Radiol 43:173-179, 1970.

63. Debnam JW, Staple TW. Osseous metastases from cerebellar medulloblastoma. Radiology 107:363-365, 1973.

64. Parkinson D, Ross RT, Shields CB. Metastatic medulloblastoma. Le Journal Canadien Des Soences Neurologiques 1:253-254, 1974,

65. Freidman HS, Mahaley MS, Schold SC Jr, Vick NA, Bullard DE, D'Souza BJ, Faletta JM, Khandekar JD, Oakes WJ, Bigner DD. The efficacy of vincristine and cyclophosphamide in the therapy of recurrent medulloblastoma. Neurosurgery 18:335-340,1986.

66. Nathanson L, Kovacs SG. Chemotherapeutic response in metastatic medulloblastoma: Report of two cases and a review of the literature. Med Pediatr Oncol 4:105-110,1978.

67. Ettinger LJ, Sinnaih D, Siegel SE, Fishman LS, Segal HD, Soni D, Bennetts GA, Schultz DH, Raphael D. Combination chemotherapy with cyclophosphamide, vincristine, procarbazine and prednisone (COPP) in children with brain tumors. J Neuro-Onc 3:263-270, 1983.

68. Van Eys J, Cangir A, Coody D, Smith B. MOPP regimen as primary chemotherapy for brain tumors in infants. J Neuro-oncol 3:237-243, 1985.

69. Spencer CD, Weis RB, Van Eys J, Cohen P, Edwards B. Medulloblastoma metastatic to the marrow. Report of 4 cases and review of the literature. J Neuro-oncol 2:223-235, 1984.

70. Chamberlin MC, Edwards MSB, Silver P, Levin VA. The treatment of extraneural medulloblastoma with a combination of Cyclophosphamide, Adriamycin and Vincristine (CAV). in press.

71. Allen JC, Walker R, Luks E, Barfoot S, Tan C. Carboplatin and recurrent childhood brain tumors. J Clin Oncol 5:459-463, 1987.

72. Thomas PR, Duffner PK, Cohen ME, Sinks LF, Tebbi C, Freeman A. Multimodality therapy for medulloblastoma. Cancer 45:666-669, 1980.

73. Pendergrass et.al. Eight drugs in 1 day chemotherapy: The rationale and results of a multidrug regimen for pediatric patients with malignant brain tumors. J Clin Oncol (in press).

74. Lowery GS, Kimball JC, Patterson RB, Raben M. Extraneural metastases from cerebellar medulloblastoma. Am. J. Pediatric Hematology Oncology 4:259-262, 1982.