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Treatment of unresectable meningiomas with the antiprogesterone agent mifepristone

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The possibility that meningioma growth may be related to female sex hormone levels is suggested by several lines of evidence. Meningiomas are twice as common in women as in men, have been observed to wax and wane with pregnancy, and are positively associated with breast cancer. A physiological explanation for these phenomena is provided by the finding of steroid hormone receptors in meningiomas. However, unlike breast cancer, meningiomas are much more commonly positive for progesterone receptors than for estrogen receptors.

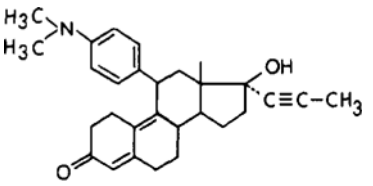
The authors initiated a study on long-term oral therapy of unresectable meningiomas with the antiprogesterone mifepristone (RU486). Fourteen patients received mifepristone in daily doses of 200 mg for periods ranging from 2 to 31+ months (≥ 6 months in 12 patients). Five patients have shown signs of objective response (reduced tumor measurement on computerized tomography scan or magnetic resonance image, or improved visual field examination). Three have also experienced subjective improvement (improved extraocular muscle function or relief from headache). The side effects of long-term mifepristone therapy have been mild. Fatigue was noted in 11 of the 14 patients. Other side effects included hot flashes in five patients, gynecomastia in three, partial alopecia in two, and cessation of menses in two. Long-term therapy with mifepristone is a new therapeutic option that may have efficacy in cases of unresectable benign meningioma.

KEY WORDS • **meningioma** • **mifepristone** • **progesterone** • **hormone therapy**

THE possibility that growth of meningiomas could be influenced by female sex hormones was originally suggested by epidemiological observations. Intracranial meningiomas are found twice as often in women as in men.[14] Several reports[3,9,19,22,36] have described an increase in meningioma size or symptoms during pregnancy, with resolution after completion or termination of pregnancy, and reappearance during successive pregnancies. An association between meningioma and breast cancer has also been noted.[11,33] Schoenberg, *et al.*,[33] studied data from the Connecticut Tumor Registry and demonstrated a significant correlation between breast cancer and meningioma (eight observed cases vs. 3.37 expected cases, $p < 0.05$). Based on data from the Los Angeles County Tumor Registry, Emry[11] confirmed a positive association for meningioma following breast cancer (37 observed cases vs. 10.5 expected cases, $p < 0.001$).

A physiological explanation for these correlations was first suggested by Donnell, *et al.*,[10] who detected estrogen receptors in four of six meningioma specimens. However, numerous later studies,[2,4,7,12,13,16,17,20,21,27,29,30,32,34,35,37–39] which examined both estrogen and progesterone receptors, determined that the hormone receptor pattern of meningioma differed markedly from that of breast cancer. While positivity for estrogen receptor is more common than for progesterone receptor in breast cancer, the opposite situation exists in meningioma. Overall, 72% of meningioma specimens have been found positive for progesterone receptor while only 31% were positive for estrogen receptor.[2,4,7,10,12,13,16,17,20,21,27,29,30,32,34,35,37–39]

Identification of the putative progesterone-receptor protein as a true receptor has been confirmed by several methods. Markwalder, *et al.*,[20] Blankenstein, *et al.*,[4] and Ironside, *et al.*,[13] have demonstrated appropriate specificity of the progesterone-binding protein through competitive binding assays. Blankenstein, *et al.*,[5] and Press and Greene[28] have also demonstrated positive immunostaining of meningioma specimens with monoclonal antibodies directed against the progesterone receptor. Blankenstein, *et al.*,[5] has further demonstrated an excellent correlation between intensity of monoclonal antibody staining and levels of progesterone



RU 486

FIG. 1. Illustration of the molecular structure of mifepristone (RU486).

receptor. In view of the frequent presence of progesterone receptors and the epidemiological correlations discussed above, modulation of progesterone levels or of the progesterone-receptor protein would seem to be a promising strategy for inhibiting meningioma growth.

Mifepristone (RU486; 11β-(4-dimethyl-amino phenyl)-17β-hydroxy-17α-(prop-1-ynyl)-estra-4,9, dien-3-one; Fig. 1) is a 19-nor steroid with high affinity for both the progesterone and glucocorticoid receptors.[1] Antiprogesterone activity requires a lower dose of mifepristone than for antiglucocorticoid effects.[1] This compound is therefore of great interest in clinical situations where a specific blockade of progesterone receptors is desired. It has been used for termination of early pregnancy[8] and may be useful for contraceptive purposes.[23]

Several *in vitro* studies have supported the possible use of mifepristone as a treatment for meningioma. Olson, *et al.*,[25] using a cell culture assay, demonstrated 18% to 36% growth inhibition by mifepristone in all three meningiomas tested. The same group,[26] using a nude mouse model, demonstrated the disappearance of implanted meningioma nodules in two of three mice. More recently, Blankenstein, *et al.*,[6] demonstrated a significant decrease in thymidine labeling index in 13 meningioma specimens treated with increasing concentrations of mifepristone.

We therefore initiated a trial of the administration of mifepristone for the treatment of unresectable meningioma. The daily oral dose chosen was similar to that used in other studies[8,23] where an antiglucocorticoid effect without a clinically significant antiprogesterone effect was required. However, in contrast to those studies, which required treatment for only a few days, the present study anticipated long-term treatment with mifepristone.

Clinical Material and Methods

Patient Eligibility

Patients with a persistent or recurrent unresectable meningioma with measurable or evaluable disease were eligible for this study. Documentation of the histological diagnosis of meningioma was obtained whenever possible; however, patients in whom biopsy might have resulted in excessive morbidity due to tumor location (optic nerve or cavernous sinus meningiomas) were eligible for the study after a review of records and diagnostic scans by one of the investigators (A.S.), a neuro-ophthalmologist experienced in the diagnosis and treatment of meningiomas in these locations. Adequate hematological reserve (white blood count $\geq$ 3000/cu mm, platelet count $\geq$ 100,000/cu mm), renal reserve (creatinine $\leq$ 2 mg%), and hepatic reserve (bilirubin $\leq$ 2 mg%) were required. All patients were ambulatory adults with a life expectancy of 12 weeks or more. Signed informed consent was obtained from all patients. This study was approved by the Institutional Review Board of the Los Angeles County-University of Southern California Medical Center.

Patients were considered ineligible if curative surgery was possible. Premenopausal females were required to have a negative pregnancy test immediately before beginning therapy and were strongly urged to use effective contraceptive methods. Patients were also ineligible if there was evidence of a second active neoplasm requiring cytotoxic chemotherapy, a serious intercurrent illness, or a history of thrombophlebitis. Patients who had undergone some other additive or ablative hormonal therapy within the preceding 8 weeks were excluded. Patients with prior cranial irradiation were eligible only if the tumor had shown definitive progression following irradiation.

Treatment Plan

All patients received a daily oral dose of 200 mg mifepristone (supplied as 200-mg tablets) throughout the course of the study. This dose was estimated to provide antiprogesterone activity without clinically significant antiglucocorticoid activity.[8,23] However, in view of the possibility of antiglucocorticoid activity resulting from this compound, all patients also received a daily oral supplement of 1 mg dexamethasone for the first 14 days of therapy. Treatment with mifepristone was planned to continue for at least 1 year.

Study Parameters and Follow-Up Period

Patients were seen every month during the 1st year of treatment and every 3 months thereafter. Complete physical and neurological examination including evaluation for subjective side effects or improvement was performed at each clinic visit. A complete blood count and serum chemistry panel were performed every 3 months, and objective tumor measurements were made every 6 months based on computerized tomography (CT) scanning, magnetic resonance (MR) imaging, or visual field examination.

Definition of Responses to Therapy

Responses to treatment were defined as follows: "complete response," complete disappearance of tumor on CT or MR studies; "tumor regression," any reduction in objective tumor measurements (preferably accompanied by subjective improvement or lessening of neurological symptoms); "stable disease," no significant change in objective parameters with no change in symptoms or neurological findings; and "progressive dis-

TABLE 1

Clinical summary in 14 patients with unresectable meningioma

Case No.	Age (yrs) & Sex	Menopausal Status	Karnofsky Performance Scale Score	Tumor Histology	Site of Tumor	Prior Therapy	Duration of Mifepristone Therapy (mos)	Best Response
1	38, M	—	90%	meningothelial	sphenoid wing	surgery	31+	regression
2	49, M	—	80%	meningothelial	cervical spinal cord	surgery, tamoxifen	8	progression
3	38, F	premenopausal	100%	cellular	cervical spinal cord	surgery	24	regression
4	66, F	postmenopausal	90%	meningothelial	petrous axis/ cavernous sinus	surgery	25+	stable
5	56, F	postmenopausal	100%	fibrous	petrous apex	surgery	27+	stable
6	61, F	postmenopausal	60%	malignant	frontoparietal/lung metastases	surgery	2	progression
7	43, M	—	80%	malignant	temporal lobe	surgery, radiotherapy	6	progression
8	63, M	—	90%	meningothelial	cerebellopontine angle/ petrous apex	surgery, tamoxifen	20	stable
9	78, F	postmenopausal	80%	cellular	cervical spinal cord	surgery, tamoxifen	3	refused further therapy
10	41, F	postmenopausal	90%	meningothelial	cavernous sinus	surgery, megestrol acetate	23+	regression
11	52, M	—	100%	unbiopsied	cavernous sinus/sphenoid ridge	none	19+	regression
12	69, F	postmenopausal	90%	fibrous	cavernous sinus/petrous apex	surgery	12+	stable
13	80, M	—	90%	unbiopsied	cavernous sinus	none	12	stable
14	23, F	premenopausal	100%	cellular	cavernous sinus	surgery	9	regression

ease," an increase of more than 25% in tumor size seen on CT or MR studies or any worsening of symptoms or neurological signs.

Results

Patient Characteristics

Fourteen patients were entered into this study between November, 1987, and May, 1989 (Table 1). Although the study population included a wide range of patient ages (range 23 to 80 years, median 54 years) most patients had an excellent Karnofsky Performance Scale score (range 60% to 100%, median 90%). Eight women (two premenopausal and six postmenopausal) and six men comprised the study group. The most common tumor histology was meningothelial or cellular (eight cases). Two patients had fibrous meningiomas and two had malignant meningiomas. Two patients were entered without biopsy; in both cases, a clinical history strongly consistent with meningioma was present and biopsy for the sole purpose of obtaining histology was considered to carry an undue risk of morbidity. The most common location of tumor was in the cavernous sinus or at the base of the brain. Three patients had meningiomas of the cervical spinal cord, and two had cerebral meningiomas. One of the two with a cerebral lesion had a malignant meningioma metastatic to the lung; the other had undergone multiple attempted resections of recurrent meningioma in a cerebral location over a period of 13 years, with progression from meningothelial to malignant meningioma. In 12 patients, prior surgical procedures had been performed. One patient had previously received radiotherapy, one had been given megestrol acetate therapy, and three patients had been administered tamoxifen.

Two patients were receiving chronic glucocorticoid supplementation at the initiation of mifepristone therapy. A third patient began glucocorticoid therapy during mifepristone treatment due to the development of a symptomatic spinal cyst. In two patients chronic thyroid supplementation had been started before the initiation of mifepristone therapy, while a third patient began thyroid supplementation for fatigue and abnormal results of thyroid function tests during mifepristone therapy. Eight patients were receiving chronic treatment with antiseizure medications including Dilantin (phenytoin sodium), Tegretol (carbamazepine), valproate, phenobarbital, and Mysoline (primidone).

Study Therapy

In this study group, daily mifepristone therapy has been delivered for periods ranging from 2 to more than 31 months. Twelve of the 14 patients have received mifepristone for at least 6 months and nine of these have received mifepristone for at least 1 year.

Responses to Therapy

Of 13 patients considered assessable for response (one patient refused further therapy), 12 had received therapy for at least 6 months and one discontinued therapy before 6 months due to progressive disease. Five of these patients experienced tumor regression (Table 2). One male patient with meningothelial meningioma of the sphenoid wing achieved minor decrease in tumor mass, as observed on a serial CT scan, accompanied

TABLE 2

Summary of patients with tumor regression in response to mifepristone therapy

Case No.	Menstrual Status or Gender	Tumor Location	Response*	
			Objective	Subjective
1	male	sphenoid wing	minor decrease on CT scan	improved extraocular muscle function
3	premenopausal	cervical spinal cord	minor decrease on MRI	disappearance of occipital headache
10	postmenopausal	cavernous sinus	minor decrease on CT scan	none
11	male	cavernous sinus/sphenoid ridge	improved visual field examination	improved extraocular muscle function
14	premenopausal	cavernous sinus	minor decrease on MRI	none

* CT = computerized tomography; MRI = magnetic resonance image.

by improved extraocular muscle function. A second male patient with an unbiopsied meningioma in the cavernous sinus/sphenoid wing experienced objective improvement in his visual field examination accompanied by improved extraocular muscle function. One premenopausal patient with a cellular meningioma of the cervical spinal cord achieved minor decrease in tumor mass, as demonstrated by MR imaging, accompanied by resolution of a tumor-related occipital headache. Regrowth of her meningioma occurred after 24 months of mifepristone therapy. One postmenopausal patient with meningothelial meningioma of the cavernous sinus demonstrated a minor decrease in tumor mass on CT scanning. An MR study in another premenopausal patient with cellular meningioma of the cavernous sinus showed a minor decrease in tumor mass. Subjective improvement tended to appear within 2 to 3 months of the initiation of mifepristone therapy while minor objective regression (decrease in cross-sectional tumor size by approximately 10%) was generally noted after 6 to 12 months.

Only three of the 14 patients had direct disease progression while undergoing therapy. One patient with a meningothelial meningioma of the cervical spinal cord had tumor progression after 8 months of therapy. The other two patients were those with the most malignant histologies. Malignant meningioma and lung metastases in one patient progressed 2 months after beginning therapy. The second patient, who had undergone multiple attempted resections of a cerebral meningioma over a 13-year period with increasing histological malignancy, had tumor progression after 6 months of therapy.

Side Effects

All 14 patients were evaluable for side effects. Long-term therapy with mifepristone was well tolerated (Table 3). The most common side effect was mild to moderate fatigue which developed in 11 patients. Both premenopausal patients experienced cessation of menses which continued during the course of treatment. Menses returned in both cases after discontinuation of treatment. Three of the six male patients developed tender palpable gynecomastia during the first several months of therapy and three of them noted intermittent hot flashes. One premenopausal and one postmenopausal patient also noted hot flashes. Two female patients noted mild transient thinning of the hair. No patient noted sexual dysfunction or a change in libido. Increase in serum cortisol and decrease in thyroxine levels were noted and may explain some of the other observations (SM Grunberg, unpublished data). Detailed analyses of hormonal parameters are presently underway.

Two patients chose to discontinue mifepristone therapy. In one patient this decision was due to increasing pedal edema after 3 months of therapy. However, review of medical records revealed that pedal edema had begun to increase prior to initiation of mifepristone therapy. One premenopausal patient chose to discontinue therapy after 9 months due to concern over cessation of menses.

Discussion

Mifepristone

Although mifepristone was originally designed and has been most extensively studied for termination of pregnancy and potential contraceptive purposes,[1,8,23] the potent activity of this agent as a progesterone antagonist and its significant activity as a glucocorticoid antagonist have raised the possibility of numerous other therapeutic applications. Nieman, *et al.*,[24] reported the case of a patient with Cushing's syndrome treated with daily oral administration of mifepristone for 9 weeks at doses ranging from 5 to 20 mg/kg/day. Improvement in clinical symptoms as well as in glucocorticoid-related endocrinological variables were noted during therapy.

Romieu, *et al.*,[31] and Klijn, *et al.*,[15] reported trials of mifepristone as second-line hormonal therapy after tamoxifen in postmenopausal patients with metastatic

TABLE 3

Side effects of long-term treatment with mifepristone

Side Effect	No. of Patients*		
	Premenopausal	Postmenopausal	Male
cessation of menses	2/2	NA	NA
hot flashes	1/2	1/6	3/6
gynecomastia	0	0	3/6
partial alopecia	0	2/6	0
fatigue	2/2	4/6	5/6

* Numbers of patients are presented as affected patients/total number of patients in that group. NA = not applicable.

breast cancer. Romieu, *et al.*, treated 22 patients with mifepristone, 200 mg/day, for periods of 1 to 3 months. Three patients achieved 50% regression of skin lesions while eight patients experienced a decrease in levels of carcinoembryonic antigen. Klijn, *et al.*, treated 11 patients and noted a partial response of lymph node metastases in one. The present study is the first report of mifepristone therapy for meningioma, a tumor for which the potential of progesterone to act as a growth factor has only recently been appreciated.

Progesterone Receptors

Progesterone modulation would be most promising for tumors in which the progesterone receptor level is high. Progesterone receptor levels could not be measured in most of our patients. Some patients were referred to our institution with recurrence or persistence of meningioma months or years after the original surgical procedure. In other patients it was impossible to obtain sufficient tissue for hormone receptor assays due to the unresectable location of the tumor itself. However, due to the high frequency (72%) of progesterone receptor positivity noted in meningiomas in multiple series over the past decade,[2,4,7,12,13,16,17,20,21,27,29,30,32,34,35,37–39] we felt that a trial of mifepristone for all patients with unresectable meningioma was reasonable.

Analysis of Results

We are encouraged by the tumor regression noted in five of the 13 evaluable patients. All five had objective signs of regression after 6 to 12 months of therapy, while three patients also experienced subjective improvement within 2 to 3 months. In this study, the criteria were not as strict as those generally used for partial response of malignant neoplasms (50% shrinkage); however, a relatively benign tumor such as meningioma might not be expected to demonstrate the rapid 50% shrinkage characteristic of a responding malignant neoplasm. In addition, tumors within the closed space of the skull or spinal cord may cause significant neurological deterioration with progression of less than 25% and may be associated with marked clinical improvement when there is regression of a similar magnitude.

Two of the three patients who directly developed progressive disease while on mifepristone therapy were those with the most malignant histologies. Lesch, *et al.*,[17] suggested that a lower incidence of progesterone receptor positivity may be seen in anaplastic meningioma. Thus, malignant meningioma may not be an appropriate histology for trials of hormonal modulation. Previous clinical studies with mifepristone have concentrated on medium-term therapy in postmenopausal patients[15,31] and short-term therapy in premenopausal patients.[8,23] We have demonstrated that extended cessation of menses in premenopausal women and gynecomastia and hot flashes in men may also be observed after long-term therapy of these patient groups.

Long-Term Therapy

The experience with our patient population indicates that long-term therapy with daily oral mifepristone for periods of 2 years or more is feasible and tolerable. All of our patients who were employed at the initiation of therapy were able to continue in their work, although some decreased their workload due to fatigue. One patient who was disabled at the initiation of therapy was able to return to work as extraocular muscle function improved and diplopia decreased. Experience with tamoxifen in breast cancer indicates that long-term therapy may be necessary for maximum effect.[18] The ability to deliver an antiprogestational agent for a period of several years may have similar implications for progesterone-dependent tumors.

Although the daily dose of mifepristone was selected so as to fall in a range that would achieve potent antiprogestational activity without severe antiglucocorticoid activity, we were concerned about the possibility of clinical glucocorticoid deficiency after chronic treatment. Klijn, *et al.*,[15] observed an increase in adrenocorticotropic hormone and serum cortisol levels in patients receiving medium-term therapy with mifepristone. No patient in our study required initiation of glucocorticoid supplementation for signs of clinical glucocorticoid deficiency. However, one patient who was glucocorticoid-dependent prior to initiation of mifepristone therapy required an increase in daily baseline glucocorticoid supplementation for relief of significant treatment-related fatigue.

Future Studies

Objective tumor regression observed during this study was minor; meningiomas may remain stable for years even without therapeutic intervention. These results must therefore be considered preliminary and will require confirmation in larger controlled studies. However, it should be noted that 11 of the patients in this trial had demonstrated objective or symptomatic progression of disease prior to study entry. Our observations of the activity of mifepristone in treating unresectable meningioma represent a fascinating correlation of *in vitro* data on tumor biology with the clinical application of an appropriately designed pharmacological agent. Increased appreciation of the role of steroidal hormones as potential growth factors in specific situations may lead to new therapeutic avenues.

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