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*Clinical Study*

# Lack of efficacy of megestrol acetate in the treatment of unresectable meningioma

Steven M. Grunberg and Martin H. Weiss
*Division of Medical Oncology, LAC USC Medical Center and University of Southern California Comprehensive Cancer Center; Department of Neurosurgery, University of Southern California School of Medicine, Los Angeles, California, USA*

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**Abstract**

The detection of hormone receptors on meningiomas raises the possibility of hormonal manipulation as a form of therapy. Since progesterone receptors are found on meningiomas more frequently and in greater amounts than estrogen receptors, manipulation of progesterone levels would be most promising. A trial of the oral progesterone agonist megestrol acetate for the treatment of unresectable meningioma was therefore performed. Megestrol acetate was administered at a dose of 40 mg four times daily which could be escalated to 80 mg four times daily. Nine patients (six meningothelial, two fibrous, and one anaplastic meningiomas) were treated for 1 to 12 months. No tumor responses were seen. However three patients required discontinuation of therapy due to deteriorating vision within 2 1/2 months. The major systemic toxicity of megestrol acetate was weight gain with a median weight gain of 14 kg for patients treated for at least 6 months. Due to the lack of efficacy and the significant toxicity noted, megestrol acetate is not recommended for the treatment of meningioma. However clinical trials of progesterone antagonists would still be of interest.

## Introduction

Both epidemiologic and biochemical evidence has suggested that meningioma growth may be hormone dependent. Meningiomas are more common in women than in men [1] and have been reported to increase in size during pregnancy [2]. Several tumor registry studies [3, 4] have demonstrated an increased risk of meningioma in patients with a prior diagnosis of breast cancer. This epidemiologic evidence led to the detection of hormone receptors on meningiomas [5]. However the pattern of hormone receptor positivity of meningiomas is markedly different from that of other hormone responsive tumors such as breast cancer. In breast cancer estrogen receptor positivity is more common than progesterone receptor positivity and the appearance of progesterone receptors depends upon the activation of estrogen receptors [6]. Meningiomas on the other hand have consistently been shown to have higher levels and frequency of progesterone receptors than of estrogen receptors [7–14]. Progesterone rather than estrogen would therefore seem to be the primary hormonal mediator of meningioma.

The most commonly employed hormonal manipulation for the treatment of breast cancer is administration of the antiestrogen tamoxifen [15]. However use of an antiestrogen would not be likely to succeed in a tumor such as meningioma where estrogen receptor positivity is rare. Indeed a pilot study by Markwalder [16] of the treatment of meningioma with tamoxifen demonstrated no significant tumor shrinkage.

Manipulation of progesterone levels would be much more likely to have therapeutic efficacy in this disease. No commercial antiprogestational agent analogous to tamoxifen is presently available. However there are several progesterone agonists with demonstrated antiproliferative activity against hormone dependent tumors. Olsen [17] using a cell growth assay and Grunberg [14] using a human tumor stem cell clonogenic assay have demonstrated that pharmacologic concentrations of progesterone can inhibit *in vitro* growth of meningioma. Use of such agents might therefore be promising.

Megestrol acetate is a progesterone agonist with clinical activity against both breast cancer and endometrial cancer [18]. We now report the results of a pilot study examining the effect of megestrol acetate therapy on unresectable meningioma.

## Methods

Eligible patients had biopsy documented measurable or evaluable unresectable meningioma. Adequate hematologic reserve (WBC $\geq 3000$, platelet count $\geq 100{,}000$), renal reserve (creatinine $\leq 2$ mg%), and hepatic reserve (bilirubin $\leq 2$ mg%) were required. Patients had to have recovered from any previous surgery, radiotherapy, or chemotherapy. Signed informed consent was obtained from all patients. Patients were ineligible who were eligible for curative surgery, who were pregnant, who had evidence of a second active neoplasm requiring systemic cytotoxic therapy or an intercurrent illness requiring immediate medical attention, or who had a history of thrombophlebitis or cranial irradiation (unless the meningioma had shown progression since irradiation). No additive or ablative hormonal therapy within the preceding 8 weeks was allowed. This study was approved by the Los Angeles County-University of Southern California Medical Center Institutional Review Board.

Treatment consisted of administration of oral megestrol acetate (Megace, supplied by Mead-Johnson). No other additive or ablative hormonal therapy was administered to the patient while on study. Treatment was initiated with oral megestrol acetate 40 mg four times daily. The dose could be escalated to 80 mg four times daily after 1 month if therapy was well tolerated. Patients were evaluated at baseline, 1 month after starting therapy, and every 3 months during therapy. CT scan or NMR scan was repeated at least every 3 months while patients were on study. Therapy was terminated if patients showed progressive disease, if patients refused further therapy, or if patients or their physicians felt that further therapy was not in their best interest.

## Results

Nine patients were entered on this study (Table 1), all of whom are considered evaluable for response and toxicity. Four patients were male and 5 were female. The median age was 40 years (range 27 to 63) and the median Karnofsky Performance Status was 90% (range 70% to 100%). All patients had biopsy documented meningioma. Six patients had meningothelial and 2 patients had fibrous meningiomas. One patient had an anaplastic meningioma with numerous mitotic figures. Progesterone receptor status was known in only 2 patients and was negative in both. In 8 patients the meningioma could not be completely resected due to location (base of brain in 7 patients and optic nerve in 1 patient). The anaplastic meningioma was unresectable due to deep recurrence after multiple surgical resections. All patients had had prior surgery. One patient had been treated with tamoxifen without response. The patient with anaplastic meningioma had received cytotoxic chemotherapy (BCNU) and radiotherapy. Patients were treated with megestrol acetate for 1 to 12 months. Five patients were treated for at least 6 months.

No responses to megestrol acetate therapy were noted. Four patients were taken off study after treatment periods of 2 1/2 months or less. The patient with anaplastic meningioma experienced growth of his tumor documented by CT scan and general clinical deterioration during the treatment period. The 3 other patients treated for short periods of time all had clinically significant decreases in

vision requiring other therapeutic interventions. One of these 3 patients in addition experienced increasing headache and tumor progression documented by CT scan, the second also had progression documented by CT scan, while the third had no change in NMR scan in spite of documented visual loss. Of the 3 patients treated for 6 months, one had therapy discontinued due to progression on CT scan, one discontinued therapy due to a decrease in vision documented by visual field examination in spite of a stable CT scan, and one patient with a stable CT scan requested termination of therapy due to weight gain. Of the 2 patients (both with fibrous meningioma) treated for 1 year, one had a slight increase in tumor size on CT scan and one requested discontinuation of therapy due to weight gain in spite of a stable CT scan.

The major toxicity of long term megestrol acetate therapy was weight gain. The 5 patients treated for 6 months or longer had a median weight gain of 14 kg (range 11 to 23 kg). Some of this excess weight was lost soon after discontinuation of therapy. Two patients noted the onset of shortness of breath and chest tightness or pain soon after escalation to 80 mg four times daily. These symptoms resolved and did not recur after deescalation to 40 mg four times daily.

## Discussion

In view of the high level of progesterone receptor positivity consistently noted in meningioma specimens, attempts to influence meningioma growth through alteration of progesterone levels would seem reasonable. Using a human tumor stem cell clonogenic assay, we [14] observed significant growth inhibition by progesterone of 4 of 10 progesterone receptor positive meningiomas. Using a cell growth assay Olson [17] also observed significant growth inhibition by progesterone of 1 of 3 progesterone receptor positive meningiomas. An *in vivo* effect of progesterone supplementation has been demonstrated by Markwalder [19] who treated 15 patients with medroxyprogesterone acetate prior to surgical resection of meningioma and noted a lower mean level of progesterone receptor positivity in surgical specimens from the treated group (15.6 fmol/mg protein) compared to progesterone receptor levels of an historical series of 58 meningioma patients (54.9 fmol/mg protein). Two clinical trials have now attempted to use high dose progesterone supplementation to decrease growth in meningioma. Jaaskelainen [20] treated 5 patients with inoperable meningioma with medroxyprogesterone acetate and noted no response after

*Table 1.* treatment of unresectable meningioma with megestrol acetate

| Patient entry number | Age/ sex | Histology | Location | Prior therapy | Length of treatment (months) | Reason for discontinuation | Weight gain (kg) |
|---|---|---|---|---|---|---|---|
| 5 | 53/M | Meningothelial | Medial sphenoid ridge | Surgery/tamoxifen | 1 | Decreased vision/ headache/progression | |
| 1 | 36/M | Meningothelial | Tuberculum sellae | Surgery | $1^1/_2$ | Decreased vision/ progression | |
| 7 | 42/M | Anaplastic | Frontal/parasagittal | Surgery/radiotherapy/ chemotherapy (BCNU) | 2 | Progression | |
| 9 | 27/F | Meningothelial | Planum sphenoidale | Surgery | $2^1/_2$ | Decreased vision | |
| 2 | 33/F | Meningothelial | Diagphragma sellae | Surgery | 6 | Decreased vision | 11 |
| 4 | 42/F | Meningothelial | Medial petrous ridge/ diaphragma sellae | Surgery | 6 | Weight gain | 20 |
| 8 | 38/F | Meningothelial | Medial petrous ridge/ diaphragma sellae | Surgery | 6 | Progression | 14 |
| 3 | 40/F | Fibrous | Optic nerve sheath | Surgery | 12 | Weight gain | 14 |
| 6 | 63/M | Fibrous | Diaphragma sellae | Surgery | 12 | Progression | 23 |

17 to 29 weeks of therapy. In the present study patients were treated with megestrol acetate for periods of up to 1 year with no tumor shrinkage noted in 9 patients.

More disturbing in the present study was the rapid visual deterioration in 3 patients requiring discontinuation of megestrol acetate within 2 1/2 months of the initiation of therapy. Increase in meningioma size seen during pregnancy may represent either cellular proliferation [21] or cellular edema [22] due to fluid retention induced by progesterone. Progesterone induced fluid retention causing cellular edema in our patients with meningioma at the base of the brain could certainly lead to sufficient swelling in a short period of time to cause a significant compromise of vision [2]. However the use of hormonal supplementation in a hormone sensitive tumor also carries the risk of being stimulatory to tumor growth rather than inhibitory. Both Jay [23] and Olson [17] have suggested that low dose progesterone may be stimulatory to meningioma growth *in vitro*. The possibility of meningioma growth causing further compromise of optic nerve function therefore cannot be excluded.

Weight gain is the most commonly reported toxicity of megestrol acetate therapy [18]. In our study weight gain was the most serious toxicity and was the reason for discontinuation of therapy by 2 of the 5 patients treated for 6 months or longer. Two episodes of shortness of breath and chest tightness were noted after escalation from 40 to 80 mg four times daily but rapidly resolved after deescalation of the dose back to 40 mg four times daily. Such a clinical picture is more consistent with dose dependent fluid retention than with an acute cardiac or pulmonary event.

Lack of efficacy and significant toxicity (including weight gain and rapid visual deterioration) make megestrol acetate an unlikely candidate for further studies in the treatment of unresectable meningioma. However a new antiprogestational agent (RU-38486) has now been shown to inhibit meningioma growth in cell culture [17] and to cause shrinkage of meningioma in a nude mouse model [24]. Further clinical trials of this antiprogestational agent, which would indeed be analogous to the antiestrogen tamoxifen in breast cancer, would be promising.

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*Address for offprints:*
S.M. Grunberg,
Division of Medical Oncology,
University of Southern California Comprehensive Cancer Center,
2025 Zonal Avenue Rm. GH 10-436, Los Angeles,
California 90033, USA