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Chemotherapy for meningiomas

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Abstract

The most efficacious treatment for meningiomas is surgery. For incompletely resected or recurrent tumors, radiotherapy can be given. However, when the meningioma is unresectable and/or all other previous treatments have failed, immunotherapy or chemotherapy may be considered for malignant tumors and immunotherapy and hormone therapy may be considered for benign ones. Various chemotherapy treatments that have shown some efficacy in individual cases include combinations of Adriamycin and Dacarbazine or Ifosfamide and Mesna. The most effective immunotherapy appears to be administration of interferon-alpha, which is relatively non-toxic and easily tolerated. However, more studies are needed to better define the roles of these agents in the management of a recurrent, unresectable, or malignant meningiomas.

Introduction

Meningiomas are usually benign tumors of middle adult life and have a female predominance. Overall, 90% of meningiomas are benign, 6% atypical, and 2% malignant. Complete surgical resection is usually curative. For incompletely resected or recurrent tumors, radiotherapy should be given. Treatments with various chemotherapeutic agents have been tried for patients with recurrent, unresectable, previously irradiated meningiomas, but they have been largely ineffective [1, our unpublished data]. However, some recent case reports have suggested that chemotherapy may have a role in some recurrent or unresectable meningiomas [2, 3]. Such chemotherapies have included combination of 5-fluorouracil, folinic acid and levamisole [2] or combination of intraarterial cisplatin with intravenous doxorubicin [3]. Administration of interferon-alpha may play a role in the managemant of unresectable recurrent meningiomas [4]. The antiprogesterone agent Mifepristone (RU486) may also prove to be very useful for therapy of recurrent meningiomas [5, 6]. In the present study the M.D. Anderson Cancer Center experience on these treatments is outlined.

Aggressive meningeal tumors

Chemotherapy is the last resort for an aggressive meningeal tumor that is unresectable or that continues to grow after the patient has undergone one or several surgical procedures and has been given the maximum radiation therapy. At the University of Texas M.D. Anderson Cancer Center, during the past several years we have used several chemotherapy regimens, mainly Ifosphamide/Mesna or Adriamycin/DTIC (Table 1), to treat approximately 15 patients who had aggressive meningeal tumors. Ifosfamide, an alkylating agent activated by microsomal liver enzymes that produce biologically-active intermediates that attack nucleophilic sites on DNA [7], is used primarily to treat sarcomas. It is administered at a dose of 2gm/m^2/day for 5 days intravenously; each cycle is repeated every 4 weeks. Because Ifosfamide may cause hemorrhagic cystitis [7], it should be used with Mesna, a chemical

Table 1. Chemotherapeutic regimens for malignant meningioma

IFOS/Mesna:	Ifosphamide, 2 gm /m^2/day, continuously IV, for 5 days Mesna, 1.2 gm /m^2/day, continuously IV, for 5 days. Cycle is repeated every 3–4 weeks. Evaluation with MRI and clinical exam are repeated after every 2 cycles.
DTIC/Adria:	Adriamycin, 90 mg /m^2/day continuously IV, for 4 days DTIC, 900 mg /m^2/day continuously IV, for 4 days. Cycle is repeated every 3–4 weeks. Evaluation with MRI and clinical exam are repeated after every 2 cycles.
IFN-alpha:	Interferon-alpha, 5×10^6 IU /m^2/day subcutaneouslyq M-W-F; MRI and cycle are repeated every 8 weeks.

compound that is reduced in the kidney to a free thiol compound that reacts chemically with urotoxic metabolites, resulting in their inactivation. Administration of 1.2 gm/m^2/day during the Ifosfamide treatment helps prevent the development of hemorrhagic cystitis. Side effects other than hemorrhagic cystitis include myelosuppression, nausea, vomiting, and alopecia [7].

Another chemotherapeutic regimen combines Adriamycin, a naturally-occurring antibiotic that causes DNA breaks, and Dacarbazine (DTIC), an alkylating drug that interferes with DNA synthesis. A dose of 90 mg/m^2/day of Adriamycin and 900 mg/m^2/day of DTIC is administered intravenously for four consecutive days. Cycles are repeated every 3 to 4 weeks, depending on the patient's blood count. An evaluation to determine the patient's response to the treatment is made every 2 cycles (every 2 months) and includes clinical examination and MRI scan. If the tumor growth is inhibited or the tumor decreases in size, the regimen is continued for approximately one year or until tumor progression occurs.

The immunotherapy most frequently recommended for meningiomas is interferon-alpha, a cytokine produced by activated lymphocytes. It is basically non-toxic to the patient in low dosages and is easily tolerated [8]. The mechanism of action of interferon-alpha includes direct cytotoxic effect, activation of natural killer cells, modulation of antibody production, antiangiogenesis, and induction of major histocompatibility complex antigens on the tumor cell surface. Each course of treatment involves subcutaneous injections of interferon-alpha, 5 million units/m^2 for three alternate days (usually Monday, Wednesday, and Friday) for 8 weeks (Table 1). A repeat computed tomography (CT) or magnetic resonance imaging (MRI) scan is then taken. If the scan indicates that the tumor is stable or reduced in size, the patient continues with the same course of therapy until tumor progression occurs. Side effects of interferon-alpha therapy are usually mild and include anorexia, dryness of skin, and a flu-like syndrome with myalgias and temperature elevation [8]. CNS symptoms of cerebellar dysfunction, confusion, and hallucinations are uncommon at these dosages [8]. A formal protocol employing the administration of interferon-alpha for recurrent inoperable benign or malignant meningiomas is currently being prepared at the U.T.M.D. Anderson Cancer Center.

Benign meningiomas

Because a number of factors suggest a hormonal relationship for these tumors, the anti-progesterone agent RU486 may be efficacious in treating benign meningiomas. Meningiomas are known to occur more frequently in women (2:1) [9, 10], appear to be associated with breast cancer [11], and grow more rapidly during pregnancy. They also are known to have progesterone receptors, glucocorticoid receptors, androgen receptors, and, in a small percentage, estrogen receptors [12–14]. The progesterone receptor is both quantitatively and qualitatively the most common steroid hormone receptor in meningioma, being found in 70% of meningioma specimens, often in the absence of estrogen receptors [15]. Furthermore, both *in vitro* and clinical studies have indicated that progestins may be modulators of meningioma growth [15–17].

RU486 is a 19-nonsteroid anti-progesterone agent that binds to the progesterone receptor with five times the affinity of progesterone. It also binds to the androgen and anti-glucocorticoid receptors, although very weakly; crosses the blood brain barrier; and is eliminated through the biliary tract. Because of its action on progesterone receptors and because progesterone receptors are predominant in

meningiomas, a pilot study of the long-term use of oral RU486 in humans was conducted at the University of Southern California Comprehensive Cancer Center on 24 (9 male; 3 pre-menopausal female; 12 post-menopausal female) patients who each received 200 mg of RU486 daily for 2 to 36 months. Most of the patients tolerated the regimen with no significant side effects. During the first several weeks, patients experienced hot flashes (9 patients), mild or severe fatigue (17 and 2 patients, respectively), gynecomastia and breast tenderness (5 patients), thinning of hair (3 patients), and skin rash (2 patients); no major side effects were noted. Menses ceased in all 3 pre-menopausal patients, 2 of whom experienced return of normal menses after discontinuance of RU486. Of these 24 patients, 6 had objective responses with decreases in the sizes of their tumors accompanied in 4 patients by subjective responses, such as decrease in headache [5, 18]. The remainder of the patients had progressive disease.

For recurrent benign meningiomas, especially those that are unresectable or multifocal, or those that occur after radiotherapy failure, other forms of treatment may be considered. *In vitro* studies have demonstrated a growth-inhibitory effect of recombinant interferon-alpha in cultured meningioma cells [19]. Currently, either interferon-alpha or RU486 is being administered experimentally. The interferon-alpha is administered subcutaneously at the same dosages as that given for malignant meningiomas. Anecdotal reports have described stabilization or response of nonresectable benign meningiomas after interferon-alpha administration [4]. As noted above, a clinical trial consisting of administration of interferon-alpha for recurrent inoperable benign and malignant meningiomas is underway at the U.T. M.D. Anderson Cancer Center.

Double-blind RU486/placebo study

Currently, the Southwest Oncology Group is sponsoring a double-blind controlled study of RU486 and a placebo. The criteria for the study are listed in Table 2. In addition to the criteria stipulated in the table, the patient must have had no previous chemotherapy for this tumor, no other malignancy, except surgically resected squamus or basal cell skin carcinoma or *in situ* cervical carcinoma, and a pathologically non-malignant meningioma.

The clinical evaluation includes a gynecologic/pregnancy exam and PAP smear for women, a thyroid function test, an AM cortisol check, and CT or MRI scans of the tumor, as well as visual fields studies if the tumor is in the base of the brain, cavernous sinus, or optic nerve or if the patient has visual symptoms. The protocol calls for the patients to be accrued for four years, with the final analysis performed after two additional years of follow-up. In addition to the usual study monitoring, one formal interim analysis is planned after 75% of accrual is complete. If at that time RU-486 is found to be superior to the placebo at the .01 level, consideration will be given to stopping the trial early and concluding that RU-486 is effective.

Conclusion

In summary, chemotherapy, immunotherapy, and hormonal therapy of meningiomas should be administered only in cases for which all the conventional treatment modalities (i.e., surgery and radiotherapy) have failed. For malignant meningiomas, interferon-alpha may have some benefit. Other alternative therapies include chemotherapy with a combination of either Adriamycin and DTIC or Ifosphamide and Mesna. For benign meningiomas, interferon-alpha or RU-486 may be beneficial.

Table 2. Criteria for inclusion in double-blind RU486/placebo study

Stratification factors
Male/pre-menopausal female post-menopausal female.
Prior radiotherapy/no prior radiotherapy
Documented progressive disease/new diagnosis following appearance of symptoms
Descriptive factors
Progesterone receptor status (<5 f mol/mg protein vs ≥5 f mol/mg protein vs. unknown)
If therapy stopped, may be reinstituted if the discontinuance was less or equal to two consecutive weeks or a total of 4 weeks in any one year.

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