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Aamir Jalal Al-Mosawi *

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Review Article

Innovative Pharmacotherapy Strategies for Benign Meningiomas: A Case Study and Review of Evidence-Based Practices

Aamir Jalal Al-Mosawi

University of North Dakota School of Medicine and Health Sciences Department of Physical Therapy.

***Correspondence Author:** Aamir Jalal Al-Mosawi, University of North Dakota School of Medicine and Health Sciences Department of Physical Therapy.

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Abstract

Meningiomas are predominantly benign, slowly growing tumors that primarily affect females and can lead to significant morbidity due to pressure effects on adjacent structures and increased intracranial pressure. This article reviews the historical context of meningioma treatment, highlights a case study of a 35-year-old female with meningioma, and explores pharmacotherapeutic options, particularly the use of hydroxyurea in combination with tamoxifen. While traditional surgical and radiotherapeutic approaches have limitations, evidence suggests that hydroxyurea may effectively induce tumor regression and manage symptoms, particularly in patients with unresectable or recurrent tumors. The proposed combination therapy aims to enhance treatment efficacy while minimizing adverse effects. This multifaceted approach underscores the importance of personalized medicine in the management of benign meningiomas, advocating for further research to optimize outcomes.

Key words: benign meningioma; combination therapy; hydroxyurea; tamoxifen

Introduction

Meningiomas (Meningeal tumors) are generally benign tumors that grow slowly and are more prevalent in females. Symptoms arise from pressure on adjacent structures or increased intracranial pressure.The first documented case of meningioma was described by Swiss physician Felix Platter in 1664, during the autopsy of Sir Caspar Bonecurtius, who exhibited behavioral changes before dying six months later. The tumor was remarkably large, likened to a medium-sized apple (Figure 1A).

Figure-1A: Felix Platter (October, 28- 1536-July 28, 1614), a Swiss physician and a pioneer of anatomy and neurosurgery of the 16th century

Historical Context

Antoine Louis performed what is believed to be the first successful surgical removal of a meningioma in 1770. In 1835, Italian surgeon Zanobi Pecchioli successfully excised a meningioma from a 45-year-old patient

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Figure-1B: Antoine Louis (February 13, 1723-May 20 1792), a French surgeon

The term "meningioma" was introduced by Harvey Cushing (Figure 1C) in 1922 to categorize various brain and spinal cord tumors [1, 2].

Figure-1C: Harvey Williams Cushing (April 8, 1869-October 7, 1939)

Patients and methods

We present a case of a 35-year-old female diagnosed with a benign meningioma in July 2019. Neurosurgeons recommended surgery but hesitated due to concerns about its potential ineffectiveness and risks. The aim of this paper is to provide expert opinion on her treatment.

Results

Initially seen on October 26, 2024, the patient reported moderate headaches radiating to her eye, impacting her sleep. Magnetic resonance imaging performed during July, 2019 revealed a homogeneous extra-axial mass in the left temporo-occipital region (20 x 15 mm) with signs of raised intracranial pressure. She was diagnosed as having benign meningioma.

Magnetic resonance venography showed that the mass was compressing the left transverse sinus with distended optic nerve sheath and partially empty sella turcica.

Previous magnetic resonance imaging studies indicated tumor growth and pressure effects on surrounding brain structures. During August 2021, magnetic resonance imaging showed a well-defined extra-axial mass originating from the left tentorium cerebelli (28 x 24 x 25 mm) with evidence of mild pressure effect on the left occipital lobe and mild mass effect at the left cerebellar lobe. There was no evidence of edema.

During November 2022, magnetic resonance imaging with intravenous contrast showed extra-axial mass (36 x 24 x 26 mm) at the left side of the posterior fossa consistent with tentorial meningioma.

During April 2023, magnetic resonance imaging showed a well-defined rounded mass (34 x 21 x 30 mm) at the left cerebellar hemisphere extending upwards and compressing left tentorium, and the mass was consistent with left cerebellar meningioma.

In response, the patient was previously treated with analgesics, dexamethasone, and acetazolamide to manage increased intracranial pressure. Despite two courses of radiotherapy leading to significant hair loss, symptoms reemerged after treatment cessation.

The patient has recently consulted us because neurosurgeons suggested the need for surgery but the were hesitated to perform it because of the fear of unrewarding outcome.

Steroids and acetazolamide have used for decades in the treatment of raised intracranial pressure [3-8].

Therefore, after reassessment, the patient was treated during the first two weeks with a combination therapy with acetazolamide (250 mg twice daily) and intramuscular synacthen (Tetracosactide) which is a synthetic polypeptide that increase adrenal cortex secretion of adrenal steroids (Hydrocortisone, cortisone). She received 1 mg injection of synacthen twice weekly.

Expert Opinion on Pharmacotherapy

While hydroxyurea has been historically employed for meningiomas, its efficacy as a monotherapy is limited [10-19]. We propose a combination of hydroxyurea and tamoxifen, supported by findings from (2021) [20-21].We

opted against the use of megestrol acetate based on the findings of Grunberg and Weiss (1990) [22], and we didn't consider the use of Temozolomide based on the findings of Chamberlain and colleagues (2004) [23]. We opted against the use of subcutaneous octreotide based on the findings of Johnson et al. (2011) [24], and we didn't consider the use of alpha interferon based on the findings of Chamberlain (2013) [25].We also didn't consider the use of mifepristone based on the findings of Sharma et al (2019) [26].

Discussion

Corticosteroids like dexamethasone have been used to address elevated increased intracranial pressure for decades but carry potential side effects such as fluid retention and impaired glucose tolerance [4-6,8]. As an alternative, we utilized intramuscular synacthen, which has fewer adverse effects [9].In 1996, Schrell and his research team from Germany discussed the World Health Organization (WHO) grading system, emphasizing that many meningiomas are grade I but can be invasive. They noted that while surgical removal often fails due to the tumor's growth characteristics, radiotherapy might not significantly reduce tumor mass but could delay recurrence. Additionally, they pointed out that surgical removal of meningiomas in the posterior fossa, cavernous sinus, posterior sagittal sinus, and petrous apex can be associated with a high morbidity and recurrence rate. They proposed hydroxyurea as a treatment option [10].

Subsequent studies have highlighted hydroxyurea's capacity to induce apoptosis in meningioma cells and suggested it can stabilize disease in patients with recurrent or unresectable tumors. Evidence from various studies indicates that hydroxyurea can lead to modest reductions in tumor size and symptom relief, with acceptable side effects.

In 1997, Schrell and his research team highlighted the experimental evidence from studies on mice suggesting that hydroxyurea can inhibit the growth of cultured human meningioma cells and meningioma transplants in mice by inducing apoptosis. They treated four patients with oral hydroxyurea (1000 to 1500 mg/daily). The patients had undergone multiple surgical resections and three of them received radiotherapy. Three patients had recurrent benign meningiomas, and one patient had malignant meningioma (Grade III/WHO).The use of hydroxyurea in a male patient who had a large sphenoid wing meningioma was associated with a decrease of tumor mass by 60% over six months. The use of hydroxyurea in a female patient who had a large meningioma of the right sphenoid wing was associated with a reduction of tumor mass by 74% over ten months. In this patient the shrinkage of the tumor mass was associated with a complete remission of the symptoms of trigeminal neuralgia within two months. Abducent paresis improved with five months.

The use of hydroxyurea in a patient who had a slowly growing meningioma was associated with a reduction of tumor mass by 15% over five months. The use of hydroxyurea in patient who had malignant left cerebellopontine angle meningioma prevented recurrence two years. Schrell and his research team suggested that long-term treatment with hydroxyurea can induce full remission of meningioma patients. Therefore, oral hydroxyurea can be a valid therapeutic option in patients with unresectable and recurrent meningiomas, which can replace radiotherapy and palliative surgery [11]. In 2000, Herbert Newton from the United States and his colleagues emphasized that meningiomas may recur in 20-50% of patients despite aggressive surgical treatment and radiotherapy. In addition, many meningiomas are not easily resectable because of deep location or nearness to sensitive structures.

They underscored that hydroxyurea; a chemotherapeutic ribonucleotide reductase inhibitor agent can decrease apoptosis in meningioma cell cultures and animal experimental models.

They treated seventeen patients (13 females, 4 males) who had unresectable or residual meningioma with oral hydroxyurea (20 mg/kg/daily). Eleven patients had neurological progression or growing tumors at the time of initiating chemotherapy. Sixteen patients were available for evaluation. They found that hydroxyurea had modest therapeutic effect against meningiomas and can be tried in patients with unresectable tumors or large residual tumors after surgery. Adverse effect included mostly leukopenia, and 9 patients (53%) required dose reductions to 250-500 daily [12].In 2002, Mark A Rosenthal from Australia and his colleagues treated fifteen meningioma patients including patients with residual tumor after surgery and progressive meningioma with hydroxyurea. Eleven patients experienced stable disease, including eight patients with progressive disease. Treatment was well tolerated, but 2 patients discontinued treatment because of skin rashes.

Mark A Rosenthal and his colleagues suggested that hydroxyurea can be used with some benefit in meningioma [13].Also in 2022, Warren P Mason from Australia and his research team emphasized that the surgical treatment of meningiomas involving venous sinuses and meningiomas of the skull base continues to be challenging. They reported the treatment of 11 females and 9 males, aged 31 to 75 years (Median age: 59 years) who had recurrent or unresectable meningiomas (12 basal, two parasagittal, and six multiple) with hydroxyurea (20 mg/kg/daily). Sixteen of the 20 patients had benign meningiomas, three had atypical features, and one patient had malignant meningioma. Eight patients including four having benign meningioma, three having atypical meningiomas, and the one who had a malignant meningioma were previously treated with radiotherapy.

All patients were experiencing tumor enlargement shown by neuroimaging studies before hydroxyurea treatment. Treatment for 8-151 weeks arrested the growth in twelve patients who had benign meningiomas, and two of these 12 patients experienced clinical improvement. Treatment was well tolerated, but one patient stopped treatment because of moderate myelosuppression.

Therefore, this study showed that hydroxyurea can arrest the growth of recurrent or unresectable benign meningiomas [14]. In 2004, Shu-xu Yang from China and his colleagues reported a study which showed that hydroxyurea have the ability to inhibit meningioma cell growth in vitro. The effect was attributed to tumor cells apoptosis [15].

In 2005, Barbara M Hahn from Germany and her research team reported the treatment of 21 patients who had progressive or recurrent meningioma, including 13 patients with benign meningiomas. Treatment included radiotherapy and hydroxyurea. Treatment associated toxicity was considered minimal, and only one patient stopped hydroxyurea because of anorexia and weight loss.Barbara M Hahn and her research team considered prolonged oral hydroxyurea treatment to be effective and safe, and can help in stabilizing the disease stabilization in most patients [16]. In 2012, Wendy J. Sherman and Jeffrey J Raizer emphasized that the use of hydroxyurea in meningioma has not yet provided satisfactorily effective option, and suggested the use of combination with other agent such as hormonal agent [17].

During the same year, Min-Su Kim from Korea and his research team highlighted the importance of meningiomas as it accounts for 18-20% of all brain tumors. They emphasized that meningiomas can have a recurrence rate of 20-50% over 10-years, despite surgical resection and radiotherapy. They also emphasized that hydroxyurea (Ribonucleotide reductase inhibitor) can inhibit meningioma cells by inducing apoptosis.

Thy reported 13 patients (4 males and 9 females) aged 32 to 83 years (Median age: 61.7 years) who had recurrent benign (WHO grade I) or II meningioma,

and were treated with oral hydroxyurea (1000 mg/square meter daily in 2 divided doses).

Ten patients (76.9%) achieved stabilization of disease. Treatment was not associated with a complete response. They suggested that long-term treatment of benign meningioma with hydroxyurea is associated with some beneficial effect against recurrence and can lead to long-term stabilization in some patients. They emphasized that hydroxyurea was well tolerated and convenient, and represents an alternative therapeutic option to repeated surgeries and radiotherapy [18].

In 2014, Joshua Gurberg from Canada and his research team emphasized the effectiveness of hydroxyurea in causing apoptosis of meningioma cells in vitro and its potential to achieve clinical stabilization of meningioma. They also highlighted the favorable side-effect profile of hydroxyurea.They reported a patient who had an operated recurrent anaplastic meningioma of the skull base who was treated by radiotherapy followed by oral hydroxyurea (25 mg/kg/day) for five months. Treatment was associated with a marked and sustained response with tumor shrinkage and cavitation which was shown on magnetic resonance imaging [19].

Although hydroxyurea has been used for decades in the treatment of meningioma, it is not very effective when used alone [10-19]. Therefore, we proposed a combination of hydroxyurea and tamoxifen supported by the evidence provided Goodwin et al. (1993) and (Altinoz, 2021) [20-21].

Based on safety and potential efficacy, the combination of hydroxyurea and tamoxifen may be a reasonable option. This combination may pose a lower risk of severe myelosuppression compared to the hydroxyurea and methotrexate combination. Additionally, tamoxifen distinct mechanism of action could provide a beneficial effect without significantly increasing hematologic toxicity. Tamoxifen mechanism could offer a different approach to inhibiting tumor growth, especially in hormone-sensitive tumors.We opted against the use of megestrol acetate based on the findings of Grunberg and Weiss (1990) [22], and we didn't consider the use of Temozolomide based on the findings of Chamberlain and colleagues (2004) [23]. We opted against the use of subcutaneous octreotide based on the findings of Johnson et al. (2011) [24], and we didn't consider the use of alpha interferon based on the findings of Chamberlain (2013) [25].

In 2011, Derek R Johnson from the United States and his research team reported the use of subcutaneous octreotide (A frequently expressed agonist of somatostatin receptors in meningioma) in patients having progressive or recurrent meningioma. Treatment was well-tolerated but was not successful in achieving failed objective tumor response [24].In 2013, Marc C Chamberlain reported a study which included 35 patients (28 females and 17 males) who had recurrent high-grade meningioma (WHO grade 2 or 3), and were treated with subcutaneous alpha interferon (10 million units/square meter) every two for 4weeks (Cycle). The study found treatment to have some activity in patients with recurrent high-grade meningiomas, but was associated with moderately toxicity [25].We didn't consider the use of mifepristone based on the findings of Sharma et al (2019) [26]. In light of these findings, the combination of hydroxyurea and tamoxifen emerges as a promising option. This approach could mitigate the risk of severe myelosuppression associated with other combinations while offering distinct mechanisms of action that might enhance treatment efficacy, especially in hormone-sensitive tumors.

Conclusion

Given the complexities of treating benign meningiomas, particularly in cases where surgical options are limited, a multifaceted pharmacotherapeutic approach is vital.

Hydroxyurea is an antitumor chemotherapeutic medication that has been used alone or in combination with other chemotherapeutic medications or radiation in the treatment of leukemias and other cancers. It has been also used to increase fetal hemoglobin concentration, and reducing the occurrence of severe crisis and decreasing the need for blood transfusions in sickle cell anemia disease.

Hydroxyurea, especially in combination with tamoxifen, represents a valuable therapeutic strategy for patients with unresectable or recurrent meningiomas. Further research is necessary to solidify these findings and improve outcomes for patients affected by this challenging condition.

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The author has the copyrights of all the sketches (Figures) included in this paper).

Conflict of interest: None.

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