Role of hydroxyurea as an adjuvant treatment after Gamma knife radiosurgery for atypical (WHO grade II) meningiomas

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Introduction

Meningioma is an extra axial tumor which is a common primary tumor affecting the CNS (20–30%). Its incidence is between 4 and 6 per 100,000 per year [1,2]. World Health Organization (WHO) categorizes meningiomas into three grades: Grade 1 so called benign meningioma, Grade 2 atypical meningioma and Grade 3 anaplastic meningioma [3]. Anaplastic meningiomas carry a particularly poor prognosis, with a median survival of 1.5 years and a 5-year mortality of 68% [5,6]. An atypical meningioma is a meningioma of intermediate grade between benign and malignant forms [7].

Surgical treatment is the primary therapy, but may be incomplete due to the tumor's location and intimate relation to surrounding structures. [2,4]. The recurrence rate even in totally resected benign tumors is between 10 and 20% after 5 years, 20–30% after 10 years, and about 50% after 20 years. In some patients, surgery may be impossible or associated with an unacceptable morbidity [4]. Long term data using definitive external-beam radiation have demonstrated prolonged tumor control comparable with that observed with surgery followed by adjuvant radiation [7]. However, radiotherapy rarely reduces tumor size and may be complicated by long term side effects [2]. Stereotactic radiotherapy (SRS) has become an alternative option to external-beam radiation for recurrent or partially resected meningiomas and for patients in whom surgery is not an option because of the tumor's location or patient comorbidities [7]. Many chemotherapeutic agents have been investigated, including adriamycin, temozolomide, dacarbazine, ifosfamide, and irinotecan. None have showed conclusive results [12,13]. Hydroxyurea is an oral antimetabolite whose main use is in the treatment of chronic myeloid leukemia. The mechanism of action appears to be inhibition of ribonucleotide reductase causing apoptosis in phase S of the cell cycle [2,6]. The drug is modestly active against meningiomas, well tolerated and induces stable disease. However, there have been no documented objective radiologic responses [4,6].

Aim of study

The aim of this study was to assess the efficacy and safety of the HU protocol after GKR for atypical (G II) meningiomas.

Patients and methods

This retrospective study is a review of 19 patients following surgery, with pathologically proven atypical meningiomas, diagnosed and reviewed according to the WHO grading system, 2016 [7]. An atypical meningioma is a meningioma of intermediate grade between benign and malignant forms, with increased mitotic activity, CNS invasion, or at least three of the following features: increased cellularity, small cells with high nuclear-to-cytoplasmic ratio, prominent nucleoli, sheeting, and foci of necrosis the different pathological features of atypical meningiomas are shown in Figs. 1 and 2.

Those patients were treated between November 2008 and April 2014 by GKR at Gamma Knife Center, Cairo, using Leksell Gamma Knife units Model C, and Perfexion (Elekta AB, Stockholm, Sweden). Patients, who had received previous external beam radiotherapy, were excluded from the study. Twenty-three patients were given hydroxyurea after GKR, the dosing schedule which was adopted in this study was mainly based on the work of Schrell et al. in 1997 [9] and Weston et al. in 2006 [2] where a unified dose of 1000 mg of HU (average 15 mg/kg/day) was given to all the patients as two 500 mg capsules daily for 12 months monitored by complete blood picture, kidney function and liver function tests.

Twelve patients refused to take the treatment or were incompliant. These 12 patients were also excluded from the study. A further four patients were lost to follow up. The residual 19 patients form...
the basis for this study. The first goal of treatment was tumor control due to the progressive nature of the disease.

Before treatment all patients had an MRI brain with contrast. On the treatment day and after application of the stereotactic frame, an MRI was performed using axial T1-weighted contrast enhanced images with 1.6 mm slices and with no inter-slice gap. On stereotactic fiducial definition, only images with a mean error of deviation of less than 1 mm were accepted. Gamma plan software, versions 9 and 10.1.1 (Elekta AB, Stockholm, Sweden) was used for dose planning. The intended prescription dose was between 10 and 16 Gy with a median of 14 Gy to the 50% isodose and with a tumor cover between 85 and 100%.

Nineteen patients were harboring 20 tumors and were available for radiological follow up for a minimum of 1 year and clinical follow up for a minimum of 2 years. Twenty tumors underwent 26 gamma knife procedures. Five tumors underwent staged treatment. Tumor volume was 0.6–38.3 cc (median 12.7 cc). The prescription dose/session ranged from 10 to 16 Gy (mean 14 Gy). The mean follow-up after completion of the hydroxyurea intake was 43 months (14–76 months).

Follow-Up

Imaging follow-up examinations using contrast-enhanced MRI were done every 3 months for the 1st year, every 6 months for the 2nd year, and then annually. Additional imaging was obtained when a patient developed new symptoms or experienced the worsening of preexisting symptoms. The patient’s history and examination findings were recorded and compared with those documented prior to treatment. A 20% or greater increase in the diameter measurements in at least 2 of the largest axes was considered tumor progression. In cases where the tumor was not sufficiently visible on regular imaging, the patient underwent MRI using the same protocol as had been used on the day of treatment. The images were then imported into GammaPlan, fused, and co-registered to the treatment images for comparison. A volume difference of more than 20% from the day of treatment was considered significant. Informed consent was obtained from all patients or their guardians.

Results

Twelve (65%) patients were females and seven (35%) were males. Age ranged from 30 to 60 years with a median of 52. Three patients had multiple tumors (meningiomatosis). All patients were operated upon prior to GK.

Tumor control was achieved in 18 out of 20 tumors where 15 tumors shrank and 3 tumors remained stable with a tumor control rate of 90%. Tumor progression occurred in 2 tumors. (at 14 and 15 months). Transient edema was observed with 6 tumors which were temporary, and no G3 or G4 myelosuppression was recorded during the hydroxyurea adjuvant therapy.

Two patients died from progression of other tumors not included in the study after 3 and 6 years. Distant tumor progression (in another intracranial location or outside the treatment field) was observed in 5 patients. In 3 patients, new tumors developed at the edge of previous craniotomy. In one patient tumor progression occurred after receiving radiosurgery for another lesion, and in another patient progression occurred in an untreated tumor that was under observation. The actuarial progression free survival and overall survival at 3 years were 89.5% and 94% respectively (see Fig. 3).

All patients received hydroxyurea, 13 patients received it for 12 months uninterrupted and 1 patient received it for 12 months but interrupted due to side effects in the form of grade II anemia. Only 5 patients received their treatment for less than 1 year (8–10 months), one of those 5 patients had grade II epigastric pain and constipation. Such side effects were temporary and were medically managed. One patient received hydroxyurea for more than 1 year (20 months).

The results of the 19 studied patients are collected in Table 1—where patient number 8 had 2 lesions.
Discussion

To the best of our knowledge, this study is the first to use this combination treatment of GKR followed by HU chemotherapy for the treatment of type II meningiomas. Even so, such work has many limitations especially being a retrospective one and the limited number of the studied patients. In 2012 Adeberg et al. published their data regarding the long-term outcome after radiotherapy in patients with atypical and malignant meningiomas. Overall survival was 81% and 53% at 5 years for atypical or anaplastic meningiomas, respectively. Progression-free survival (PFS) was 95% and 50% for atypical and 63% and 13% for anaplastic tumors at 2 and 5 years [17].

Gamma knife radiosurgery is considered the best radiation option for meningiomas and was reserved in the past years for the smaller volume lesions with more and more data published for treating larger meningiomas [16]. Wang et al. in 2016 published a retrospective analysis of 46 patients with atypical or anaplastic meningiomas treated with postoperative GKR. The 1, 3, and 5-year local tumor control was 91.1%, 59.3%, and 39.5%, respectively, for WHO grade II. The management of atypical meningiomas with chemotherapy has not been a standard of care even after many phase 2 trials have been published over the past 20 years [8–10], and [12]. One retrospective study suggested that adjuvant treatment after incomplete resection of atypical meningiomas is associated with longer PFS than conservative treatment. However, there was no difference in PFS between Hydroxyurea and radiotherapy after surgery [18].

A pilot study was published in 2005 which discussed the treatment of progressive or recurrent meningiomas with hydroxyurea and concurrent 3-D conformal radiation and the majority of the patients (13/21) were G I meningioma, four cases were atypical, and 4 were of unproven pathology. They showed tumor stabilization in 14/21 patients only and none of the cases showed tumor regression [14].

In 1997, Schrell and his colleagues were the first to report dramatic tumor reduction of meningioma following the use of hydroxyurea [8], and in 2000, Newton et al. reported that 14 out of 16 cases achieved stable disease with very little overall toxicity [9].

Another more recent study that used hydroxyurea for recurrent surgery and radiation refractory high-grade meningioma reported very limited activity of hydroxyurea and questioned its effectiveness [3].

The results of some previous studies that used hydroxyurea for the treatment of meningioma are listed in (Table 2) and are compared the data of the current study regarding the radiological response to treatment.

The protocol was well tolerated with no G III or G IV toxicities and none of the studied cases needed to be withdrawn from the study due to toxicity.

This toxicity profile was better than those reported by Weston et al. [2] and Loven et al. [15] where many severe hematologic toxicities were the cause for treatment discontinuation. This could be attributed to the fixed low dose used in our study.

Conclusion

The results of the current study suggest the safety and efficacy of HU following GKR with stabilization or shrinkage of atypical (grade II) meningiomas. This protocol may achieve tumor control considering the small cohort of patients. Larger randomized and double-arm studies are required to confirm the possible role of hydroxyurea in the management of those tumors.

References


