Flutamide as a preoperative treatment in juvenile angiofibroma (JA) with intracranial invasion: Report of 7 cases

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OBJECTIVE: **To determine the efficacy of flutamide as a tumor reduction factor in patients who have juvenile angiofibroma (JA) with intracranial invasion.**

DESIGN: **A longitudinal, prospective, experimental, self-controlled pilot study.**

MATERIAL AND METHODS: **Seven consecutive patients with JA were enrolled in the study. CT scan with measurements of the tumor was performed before and after the treatment with flutamide, and the results were compared.**

RESULTS: **The biggest reduction in tumor size was 11.1%. All patients underwent surgical resection, and the bleeding was similar to patients without flutamide. No statistically significant difference was found between the measurements before and after the flutamide administration.**

CONCLUSIONS: **Despite the fact that there is a report of the efficacy of flutamide in the literature, we did not find advantages in using it in patients with JA. However, and due to the very small number of patients enrolled, we think that more studies are required.** (Otolaryngol Head Neck Surg 2004;130: 466-9.)

Juvenile angiofibroma (JA) is a histologically benign, highly vascular tumor of the nasopharynx, which commonly presents in male teenagers, and its main manifestations are nasal obstruction and profuse epistaxis. It arises at the lateral wall of the nasopharynx and tends to invade the choana, into the nasal cavities and paranasal sinuses, through the sphenopalatine foramen to the pterygopalatine and infratemporal fossae, as well as the orbit and cheek. If the tumor erodes the skull base, it may grow into the cranial cavity.

There are a number of theories to explain the etiology of the tumor, such as the presence of hormonal receptors at the cell surface and cytosol of the tumor or hormonal disorders in these patients (although still controversial).[1] Martin et al, in 1948,[2] and Schiff in 1959,[3] reported the use of sex hormones, and they demonstrated that estrogens could induce a reduction in the size and vascularity of the tumor. However, preoperative estrogen therapy is not currently used because of the variable effect of the hormones on the tumor, the delay of the definitive surgical procedure, the secondary feminizing effects, and the risk of cardiovascular complications.

In vitro reports have demonstrated that there is an increase in the growth rate of the tumor when testosterone is added, and that is why some research has centered on the effects of androgen receptor blockers, such as ciproterone and flutamide.

The hallmark of the treatment of JA is surgery, and a good approach is mandatory, as are different techniques to lessen and control bleeding. Digital subtraction angiography with preoperative embolization may reduce bleeding. Hypotensive techniques and more accurate surgical approaches make possible the total resection and cure of large tumors, even those with intracranial involvement. In the past, large tumors were only treated with radiation therapy. This method may be hazardous in benign masses, because malignant transformation has been reported.[4,5]

In a series of 10 patients treated with chemotherapy at the Hospital Infantil de Mexico Federico Gomez by Dr Martinez-Avalos (with 5-FU, folinic acid, and prednisone), they did not find significant response in the reduction of the tumor size (personal communication). This fact agrees

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Table 1. The Chandler staging system for juvenile angiofibroma

Stage	Description
I	Tumor limited to nasopharynx
II	Extension to nasal cavity and/or sphenoidal sinus
III	Involvement of one or more maxillary or ethmoidal sinus, pterigomaxillary fossa, infratemporal fossa, orbit, or cheek
IV	Intracranial extension

with the reports in the literature.[6] Farag et al,[7] in 1987, focused on the hormonal dependence of the tumor, and he found androgen-specific receptors on the tumor tissue of 7 patients. Johnsen et al demonstrated tumor growth after administration of testosterone and its reduction with estrogen therapy.[8]

The use of an androgen blocker might seem a logical alternative. Flutamide, a nonsteroidal antiandrogen drug administrated orally, is widely used in the treatment of cancer of the prostate.[9] Gates et al reported 5 patients treated with flutamide in order to induce regression of the JA, and they found an average reduction of 44% in 4 of them.[10]

Several staging systems have been proposed for the classification of this tumor, with prognostic and therapeutic purposes. The most commonly used in our department was described by Chandler in 1984[11] (Table 1).

Because most of the cases of JA seen at the Department of Otolaryngology–Head and Neck Surgery of the General Hospital of Mexico are staged as Chandler IV (with intracranial extension), it is important to find alternative choices in order to reduce the morbidity during and after surgical resection. We found in the literature only one report regarding the use of flutamide as an inductor of regression of JA prior to surgery, so we decided to try this choice on the subset of patients.

MATERIAL AND METHODS

An experimental, longitudinal, prospective study with auto-controls trial was performed with the approval of the Ethics and Research Board—General Hospital of Mexico. Our objective was to determine the efficacy of flutamide as preoperative treatment on JA stage IV of the Chandler system, with the following hypothesis:

Hypothesis 1: Flutamide induces regression of the JA.

Hypothesis 0: Flutamide does not induce regression of the JA.

The inclusion criteria were: patients of any age who accepted to take part in the study, patients with clinical and computed tomography (CT) diagnosis of JA stage IV of the Chandler system. Exclusion criteria included: patients who did not accept taking part in the study, patients with JA but Chandler staging less than IV, patients with known hypersensibility to flutamide. Finally, the elimination criteria were: patients who present any sign of hypersensibility or hepatic damage during flutamide administration and patients who decided to withdraw.

All patients admitted in this study presented at our department and were assessed as follows: complete history and physical examination; signed consent; complete blood cell count, liver function tests, and determination of serum levels of testosterone; CT scan of nose and paranasal sinuses, simple and enhanced, with tumor measurements prior to flutamide administration; and digital subtraction angiography were obtained.

The patients were given a 3-week supply of flutamide: 125 mg 4 times a day, orally. At the end of the treatment, complete blood cell count, liver function tests, and determination of serum levels of testosterone; CT scan of nose and paranasal sinuses, simple and enhanced, with tumor measurements at the end of the treatment; and digital subtraction angiography with tumor embolization were obtained.

CT Measurements

The tumor volume measurements were performed as reported by Gates et al,[10] by an expert radiologist in a blinded fashion. They were calculated on a computer digitizing board. This was done on the basis of a 5-mm-thick CT scan section with contiguous 5-mm section spaces. The calibration squares for each group each time were

Table 2. Patient features

Case	Age	Sex	Tumor volume pretherapy (cm^3)	Tumor volume post-therapy (cm^3)	Reduction percentage
1	15	Male	195.8	177.3	9.5%
2	18	Male	218.1	205.9	5.6%
3	14	Male	184.6	170.3	7.75%
4	16	Male	243.8	216.9	11.1%
5	18	Male	261.3	248.8	4.8%
6	17	Male	187.2	172.6	7.8%
7	11	Male	239.9	225.4	6.1%

constructed with equal sides calibrated to 5 cm. Each figure group was then scaled the same as the square so that the area of its calibration square was 25 cm^2. Next, the area of each section in the group was computed and summed to produce the total section area. Each calibration was done independently and blinded as to before and after treatment; with a κ value of 90. Each section was measured on 2 separate occasions and the results averaged.

Statistical Analysis

Central tendency and dispersion measures and Student's *t* test were performed with SPSS 11.0 for Windows (LEAD Technologies, Chicago, IL). Statistical significance was established at the $P < 0.05$ level.

RESULTS

Seven patients were included on this study; their ages ranged from 11 to 18 years (mean 15.6 years). All of them were males with tumors stage IV, using the Chandler system (Table 2). In this study, measurement results show a maximum tumor reduction of 11.1%. All the patients underwent surgical resection of the angiofibroma via facial degloving, except for case #7, who had a combined approach with a biparietal craniotomy. In patients 1, 2, 3, 4, and 7 the tumor was totally resected, but in patients 5 and 6 we found evidence of residual tumor, mainly at the parasellar area and pterygomaxillary fossa. The bleeding ranged from 400 cc to 11,200 cc, which is similar to patients without flutamide treatment at our department. None of these patients died during or after the surgical procedure, and no secondary effects were found.

The tumor volume in group 1 (pretherapy group) showed the following features: mean, 218.67 cm^3; standard deviation, 30.48; and range, 76.69.

In group 2 (post-therapy group), the findings were as follows: mean, 202.45 cm^3; standard deviation, 30.147; and range, 78.5.

At the Student's *t* test, we found a *t* value of 1.001 with 12 degrees of freedom, for a *P* value greater than 0.05, which is not significant, so we had to reject our hypothesis and accept the null one.

DISCUSSION

As a pilot study, no statistical methods were used to determine the number of patients required to meet the trial's objective. The small number of patients is one of the most important weaknesses of this study, because false negative results may be found. However, the principal aim of pilot studies is to open new doors for research when a field of science is poorly explored.

Flutamide interferes with the binding of testosterone in animals and humans, and its chemical designation is 4'-nitro-3'triflouro-methylisobutyranilide. It does not inhibit pituitary gonadotropin production or steroidogenesis in the gonads or adrenal glands. Plasma testosterone levels actually increase during flutamide administration. Its most common side effects are breast tenderness and gynecomastia, but they disappear at the end of therapy. Occasional nausea may be present, sexual activity is not affected, and a transient elevation of liver enzymes has been reported. Gates, in 1992, induced regression of JA using this drug.[10]

We found that there was no statistical difference between the 2 groups regarding the tumor volume

with or without flutamide administration. Many patients with JA seek medical attention at our institution late in the course of the disease. Therefore, a high percentage of them are detected on stages III–IV according to the Chandler staging system. This kind of patient represents a therapeutic challenge everywhere, and that is why a reduction of tumor size could mean a reduction in the incidence of intraoperative and postoperative complications, such as bleeding. We have tried to manage them with chemotherapy and radiation therapy with poor, if any, results.

Based on the results reported by Gates et al, where 44% of tumor reduction was found in 4 of 5 patients, we decided to use this alternative. Our study shows poor results with the use of flutamide in patients with JA with intracranial extension. We do not know if the tumor size has any influence on its response to the drug, and this could be the cause of the lack of response of our patients.

We conclude that flutamide has no effect on the tumor size of JA, and does not show any advantage at time of surgery. We could not reproduce the results of Gates et al, so we believe that more studies are required.

REFERENCES

1. Hagen R, Romano G. Juvenile nasopharyngeal fibroma: Androgen receptors and their significance for tumor growth. Laryngoscope 1994;104:1125-9.
2. Martin H, Erlich HE, Abels JC. Juvenile nasopharyngeal angiofibroma. Ann Surg 1948;129:523-36.
3. Schiff M. Juvenile nasopharyngeal angiofibroma. A theory of pathogenesis. Laryngoscope 1959;69:981-1016.
4. Chen KT, Bauer FW. Sarcomatous transformation of nasopharyngeal angiofibroma. Cancer 1982;49(2):369-71.
5. Makek MS, Andrews JC, Fisch U. Malignant transformation of a nasopharyngeal angiofibroma. Laryngoscope 1989;99(10):1088-92.
6. Goepfert H, Cangir A, Lee Y. Chemotherapy for aggressive juvenile nasopharyngeal angiofibroma. Arch Otolaryngol 1985;111(5):285-9.
7. Farag MM, Ghanimah SE, Ragaie A, et al. Hormonal receptors in juvenile nasopharyngeal angiofibroma. Laryngoscope 1987;97:208-11.
8. Johnsen S, Kloster JH, Schiff M. The action of hormones in juvenile nasopharyngeal angiofibroma. Acta Otolaryngol (Stockhl) 1965;61:153-60.
9. Surfin G, Coffey DS. Flutamide: Mechanisms of action of a new nonsteroidal antiandrogen. Invest Urol 1976;13: 429-34.
10. Gates GA, Rice DH, Koopman CF, et al. Flutamide induced regression of angiofibroma. Laryngoscope 1992; 102(6):641-4.
11. Chandler J, Goulding R, Moskowitz L, et al. Nasopharyngeal angiofibromas: Staging and management. Ann Otol Rhinol Laryngol 1984;93:322-9.