ADJUVANT THERAPY WITH FLUTAMIDE FOR PRESURGICAL VOLUME REDUCTION IN JUVENILE NASOPHARYNGEAL ANGIOFIBROMA

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Abstract: *Background.* Although 2 studies totaling 11 cases have indicated some benefit of anti-androgen treatment with flutamide on juvenile nasopharyngeal angiofibroma (JNA), it is not part of contemporary practice.

Methods. Our approach was through a prospective, single-arm, before-and-after study, in which 20 patients with advanced JNA (Radkowski stage IIB–IIIB) were administered flutamide (per oral: 10 mg kg^{-1} day^{-1} × 6 weeks) prior to surgical excision. Pretherapy and posttherapy tumor volume measurements were established by MRI. Periodic assessments were recorded of liver, kidney functions, testosterone levels, and secondary sexual characteristics.

Results. Prepubertal and postpubertal cases responded differently ($p < .05$). Prepubertal cases had inconsistent and minimal responses; 13/15 postpubertal cases demonstrated measurable volume reduction (mean, 16.5%; maximum, 40%). Two cases with optic nerve compression had visual improvement. Volume reduction correlated with serum testosterone level ($r = .53$; $p < .05$). No significant toxicity was noted, with the exception of transient breast tenderness.

Conclusions. Prepubertal and postpubertal patients differ in their response to flutamide. In postpubertal patients, 6 weeks preoperative use is safe and leads to partial tumor regression. Tumor regression from adjacent vital structures may facilitate surgical excision and limit morbidity. © 2011 Wiley Periodicals, Inc. *Head Neck* **33:** 1747–1753, 2011

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The management of juvenile nasopharyngeal angiofibroma (JNA) remains challenging. Surgical excision is the prime treatment modality, but is associated with morbidity and a high recurrence rate. Radiation therapy has been used for intracranial disease, but its application for a benign tumor in adolescents is necessarily controversial.

The exclusivity of JNA to males has pointed toward an obvious hormonal influence, and early workers noted increased tumor growth with testosterone and a regression with estrogens.[1–3] Diethylstilbesterol, an estrogen analog, was previously used to bring about tumor regression,[2,3] although it is not part of current practice because of its feminizing effects and a perceived risk of cardiovascular disease. Further, estrogen treatment led to suppression of gonadotropin release by the pituitary and consequent suppression of testosterone secretion; it remains unclear as to whether the effect of estrogen was by a direct action on the tumor or secondary to the decrease in gonadotropin and testosterone levels.

Recent years have seen a greater understanding of the sex-hormone receptors present on the tumor.[4–6] Specific receptors to both testosterone and dihydrotestosterone (DHT) have been noted, with a greater affinity being demonstrated to DHT. Flutamide (2-methyl-*n*-[4-nitro-3{trifluoromethyl}phenyl] propanamide) is an orally active nonsteroidal androgen antagonist (NSAA), which is free of the feminizing effects of previous therapies. It is a pure anti-androgen compound, with no partial agonistic effects. No suppression of gonadotropin secretion is thus noted; rather the blockade of negative feedback of testosterone on gonadotropin secretion leads to increased levels of gonadotropins and testosterone.[7,8] The loss of libido and sexual potency noted with the previous steroidal androgen antagonists is therefore significantly mitigated,[8] and the drug has found wide usage in the treatment of prostate cancer and benign prostatic hypertrophy (BPH). It has a good safety profile and has been recommended for use in adolescents and children for conditions such as congenital adrenal hyperplasia, hirsutism, and acne.[8–12] Common reported

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Table 1. Distribution of cases in accord with stage.

Stage*	Description	No. of patients
I		
IA	Tumor limited to posterior nares and/or nasopharyngeal vault	—
IB	Tumor involving the posterior nares and/or nasopharyngeal vault, with involvement of at least 1 paranasal sinus	—
II		
IIA	Minimal lateral extension into the pterygo-maxillary fossa	—
IIB	Full occupation of the pterygo-maxillary fossa, with or without superior erosion of the orbital bones	1
IIC	Extension into the infratemporal fossa or extension posterior to the pterygoid plates	5
III		
IIIA	Erosion of the base of skull (middle cranial fossa/base of pterygoids) minimal intracranial extension	6
IIIB	Extensive intracranial extension, with or without extension into the cavernous sinus	8

*In accord with Radkowski et al.[18]

side effects include nausea, hepatotoxicity, and mild breast tenderness[8,12] (ascribed to increased testicular production of estrogen). It has been recommended that liver functions be periodically assessed during therapy.[13]

Two previous studies have explored the use of flutamide in JNA,[14,15] but with conflicting recommendations. An initial study by Gates et al[14] noted mean tumor volume reduction of 29% in 5 cases with a 6-week treatment course and recommended its use. A subsequent report by Labra et al[15] with 6 cases noted very modest responses (mean reduction, 7.2%); thus they did not support the use of flutamide and recommended further studies. Current opinion and reviews in the literature do not display enthusiasm for its use.[16,17] Nonetheless, it is the authors' belief that presurgical tumor regression, if achieved by flutamide, and even if modest, may nevertheless have a significant impact in reducing surgical morbidity in advanced JNA, especially in cases with intracranial extension.

The present study is a prospective single-arm phase II evaluation of the efficacy and safety of flutamide, used as adjuvant presurgical therapy, with the intent of reducing JNA tumor size, in 20 cases recruited from 2006 to 2008.

MATERIALS AND METHODS

Study Design. Prospective, single-arm, and before-and-after evaluations of the efficacy and safety of flutamide were carried out. Flutamide was used as adjuvant presurgical therapy in advanced JNA, with the intent of reducing tumor size and facilitating surgical excision. Institutional Review Board approval was obtained. A control arm/placebo arm was not included because ethical considerations did not allow for definitive treatment to be delayed without a reasonable expectation of improvement.

Case Group. Patients with advanced JNA presenting in the period from September 2006 to December 2008 were counseled for inclusion in the study. Following informed consent, all consenting cases had an initial pretherapy biochemical screen inclusive of hematology, liver, and kidney function tests. In all, 22 patients were screened and 2 patients were excluded, 1 patient with elevation of liver enzymes and 1 patient with a scrotal hydrocele. Recruitment was restricted to cases with advanced disease (Radkowski stages IIC, IIIA, and IIIB). One case with recurrent stage IIB disease following 2 previous surgical excisions was also included.

The initial diagnosis of JNA was based on the typical radiological extensions and the described radiological signs (bowing of the posterior maxillary wall, expansion of the pterygo–maxillary fissure, erosion of the base of the pterygoid process, erosion of the floor of the sphenoid sinus, salt and pepper appearance on the MRI). All cases have since had surgical excision and histological examination has confirmed the diagnosis in all.

Twenty patients were recruited. All were males, with age ranging from 10 to 25 years (mean, 15.7 years). Seventeen patients were previously untreated, whereas 3 patients presented with recurrent tumors following previous surgical excisions. Tumor staging was done in accord with Radkowski classification.[18] Six cases were staged as stage II, and 14 cases as stage III (intracranial extension) (Table 1).

Intervention. Flutamide was administered for a 6-week course (10 mg kg^{-1} day^{-1} in 3 divided doses). The 6-week treatment duration was guided by the literature, wherein the report with 6-week treatment[14] noted greater reductions than those of the report with 3-week treatment.[15] It was undertaken that flutamide therapy would be discontinued should any case develop alteration of liver or kidney functions, hypersensitivity reaction, or significant alternate toxicity during the treatment.

Surgical excision was undertaken at the completion of the 6-week flutamide course.

Observation Schedule. Prior to initiation of flutamide therapy, all cases had baseline serum

biochemistry testing, secondary sexual characteristics evaluation, preintervention testosterone level evaluation, and tumor volume assessment by MRI.

Liver and renal functions were evaluated biweekly during treatment.

Secondary sexual characteristic evaluation was undertaken, guided by the supervision of a pediatric endocrinologist, and included breast examination (for tenderness and gynaecomastia), genitalia examination (Tanner staging), stretch penile length, and testicular volume assessment. All examinations were repeated at mid treatment (3 weeks), at end treatment (6 weeks), and at 3 months and 6 months from initiation of treatment. Testosterone levels were repeated on completion of the 6-week course of flutamide and after 3 months of completion of therapy.

Tumor volume assessment by MRI was undertaken at initial presentation and on completion of the 6-week course of flutamide. MRIs were obtained on a 1.5-Tesla scanner (Siemens Sonata/Avanto, Erlangen, Germany) using head coils. Spin echo sequences (T1- and FSE T2-weighted) in the axial plane with additional sagittal and coronal images were obtained. Further contrast-enhanced images (T1-weighted) were obtained with intravenous gadopentate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ) at a dose of 0.1 mmol/kg. Data acquisitions were undertaken with 4-mm slice thickness and 0-mm interslice gap.

The tumor volume was calculated by the Manual trace method. The assessing radiologist was blinded to the timing of the scan (pretreatment or posttreatment). The tumor was manually outlined in each successive image using a track ball, and area measurements per image were automatically calculated by the MR console software. The area measurements from all sections were then summated, and the total tumor volume was obtained by multiplying the summated area by the section thickness.

Study End-Points. Pretherapy and posttherapy volume measurements were compared, and the percentage volume change was calculated. A value of >5% was arbitrarily predefined as depicting measurable change.

RESULTS

Tolerance. No major side effects were noted, although 5 patients reported breast tenderness; however, this proved transient and regressed after completion of treatment. No case developed gynaecomastia with the 6-week treatment regimen. No other abnormality was noted in the assessment of secondary sexual characteristics. No alteration of liver or kidney functions was noted, nor did any case develop a hypersensitivity reaction to flutamide. All cases completed the 6-week treatment regimen at the prescribed dosage.

Table 2. Pretreatment and posttreatment tumor volumes and percentage reduction in tumor volume.

Serial no.	Age, y	Tumor stage	Volume, cm^3		% volume reduction
			Pretherapy	Posttherapy	
1	20	IIIA	70.2	65.3	7%
2	11	IIC	90.8	85.8	6%
3	14	IIC	101.8	65.9	35%
4	12	IIIB*	32.7	28.9	12%
5	15	IIIB	146.8	97.4	34%
6	14	IIIA	60.4	57.0	6%
7	16	IIIA	135.8	127.5	6%
8	19	IIC	68.2	57.8	15%
9	25	IIIB	63.8	55.1	14%
10	12	IIIB	103.0	111.4	−8%
11	12	IIIA	190.2	242.9	−28%
12	14	IIIB*	232.7	191.5	18%
13	15	IIIA	63.8	64.8	−2%
14	15	IIIB	64.7	48.7	25%
15	19	IIIB	57.3	55.1	4%
16	18	IIC	130.5	97.0	25%
17	17	IIIA	61.9	37.0	40%
18	15	IIIB	114.8	98.3	14%
19	21	IIIB	54.7	50.8	7%
20	10	IIB*	13.4	12.4	7%

**Cases 4, 12, and 20 were recurrent tumors. Staging as depicted is based on the tumor extent following recurrence.*

Volume Reduction. The pretherapy and post-therapy tumor volume for each patient and the percentage reduction in volume for each patient are listed in Table 2. Sixteen of 20 cases had measurable decrease (>5%) in tumor volume (Table 2, Figures 1A and 1B). Five patients had >25% reduction in tumor volume, and another 5 patients had volume reduction ranging from 10% to 25%. Two patients had an increase in tumor volume of >5%.

The maximum reduction in tumor volume noted was 40%.

Subjective improvements indicated by an improvement in the nasal airway and decreased frequency of epistaxis were reported by 17 and 15 patients, respectively. Two patients with recent onset visual loss and visual field deficits secondary to optic nerve compression demonstrated improvement.

In all 5 patients with very marked tumor regression (≥25%), the final surgical approach that was undertaken turned out to be more conservative than the approach planned at initial presentation. Three patients with stage IIC disease (case nos. 3, 14, 16) and extensive infratemporal fossa extension were initially planned for the lateral rhinotomy approach, but following postflutamide tumor regression, were finally managed by the midfacial degloving approach. Similarly, 1 patient with initial stage IIIA disease (case no. 17) had a conversion from the maxillary swing approach to lateral rhinotomy, and 1 patient with initial stage IIIB disease (case no. 5) had a conversion from the initially planned preauricular–subtemporal–infratemporal approach (with temporal craniotomy) to a maxillary swing excision and no craniotomy. A

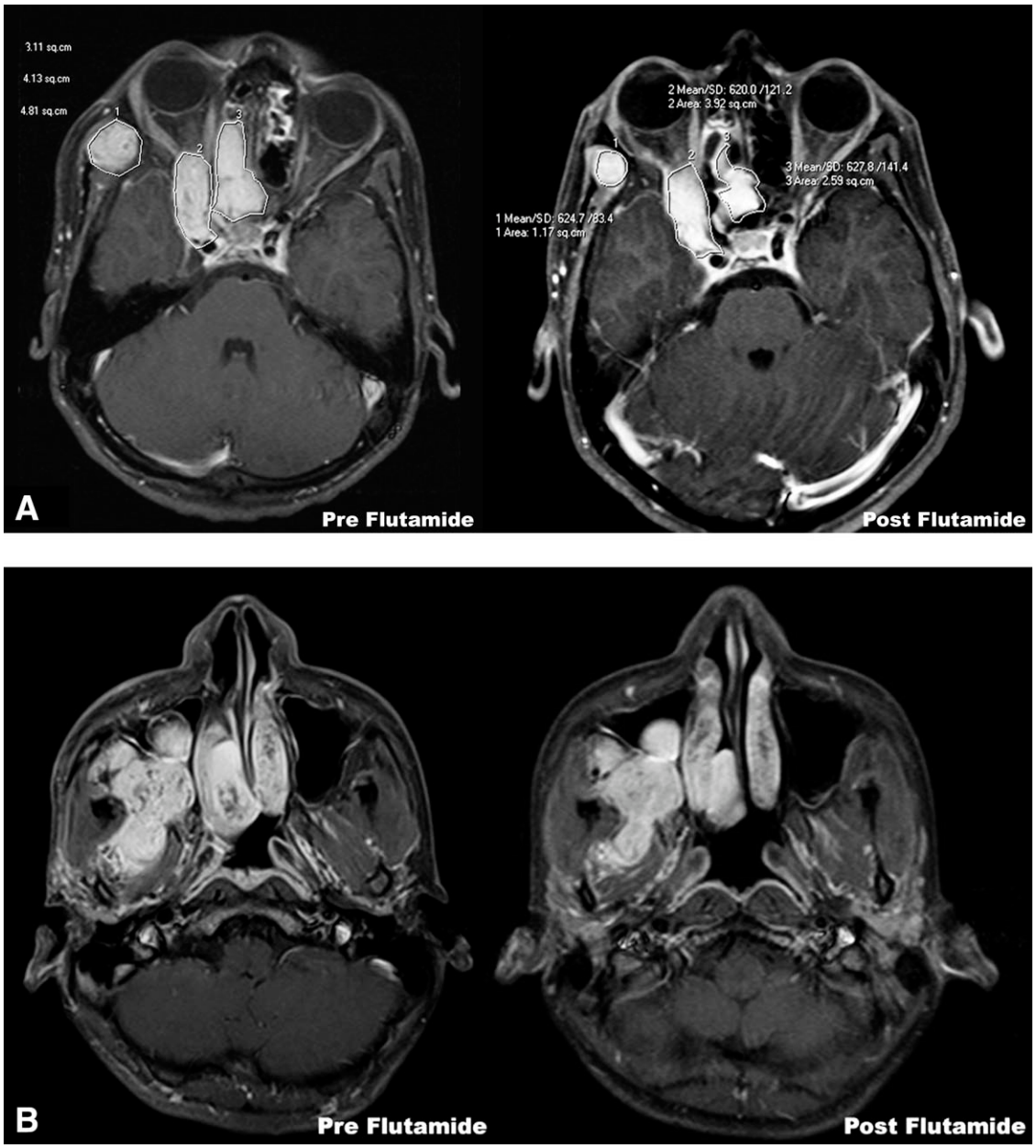

FIGURE 1. **(A)** Pre- and postflutamide axial MR images (stage IIIB juvenile nasopharyngeal angiofibroma [JNA], scans at level of internal carotid artery). Postflutamide tumor regression is noted in the ethmoids, temporal fossa, superior orbital fissure, and middle cranial fossa. **(B)** Pre- and postflutamide axial MR images (stage IIC JNA, scans at level of fossa of Rosenmuller). Postflutamide tumor regression is noted in the posterior nose and the infratemporal fossa.

facial incision was thus avoided in 3 patients, and a formal craniotomy in 1 patient.

The pretherapy testosterone levels (normal postpubertal range, 1.95–11.38 ng/mL) and the subsequent levels following treatment are listed in Table 3. Cases are segregated as prepubertal and postpubertal based on their age and testosterone levels. A marked difference is noted in the response to flutamide in the prepubertal patients (mean reduction, −2.3%), compared with the postpubertal cases (mean reduction, 16.5%; $p = .04$, Mann–Whitney test). Two prepubertal cases had significant tumor progression while on flutamide. The percentage volume change for the prepubertal and postpubertal groups is depicted graphically in Figure 2.

A positive and statistically significant correlation is demonstrated between the pretreatment testosterone level and the degree of volume reduction (Pearson's correlation coefficient, $r = .53$, $p < .05$; $R^2 = 0.28$; Figure 3). The regression coefficient of pretreatment testosterone on percentage volume reduction is 2.77 (95% confidence interval [CI]: 0.58–4.95; $p = .016$).

Table 3. Testosterone levels for individual patients as assessed pre- and post-therapy and percentage volume reduction.

Serial no.	Age, y	Testosterone level, ng/mL*			Puberty	% volume reduction
		Pretherapy	6 weeks therapy	3 months posttherapy		
1	20	6.84	21.20	7.28	Postpubertal	7%
2	11	0.18	0.10	0.15	Prepubertal	6%
3	14	6.19	NA	11.43	Postpubertal	35%
4	12	0.11	0.15	0.48	Prepubertal	12%
5	20	3.77	12.04	10.12	Postpubertal	34%
6	20	2.70	1.73	2.10	Postpubertal	6%
7	20	7.03	5.23	5.75	Postpubertal	6%
8	20	7.57	8.59	7.70	Postpubertal	15%
9	20	6.63	7.84	9.95	Postpubertal	14%
10	20	0.14	0.07	0.24	Prepubertal	−8%
11	20	0.10	0.24	0.20	Prepubertal	−28%
12	20	7.06	7.62	6.96	Postpubertal	18%
13	20	5.83	8.59	NA	Postpubertal	−2%
14	20	5.95	9.90	8.00	Postpubertal	25%
15	20	3.81	6.92	8.49	Postpubertal	4%
16	20	6.35	10.58	12.31	Postpubertal	25%
17	17	8.37	10.82	9.90	Postpubertal	40%
18	15	1.98	2.20	5.50	Postpubertal	14%
19	21	7.14	11.52	14.43	Postpubertal	7%
20	10	0.21	0.31	0.00	Prepubertal	7%

Abbreviation: NA, not available/not tested.
**Postpubertal normal range: 1.95–11.38 ng/mL*

A trend was noted for testosterone levels to rise with administration of flutamide, but this was not consistent (posttherapy testosterone/pretherapy testosterone ratio: mean, 1.47; range, 0.5–3.2). Testosterone levels tended to return toward lower levels on cessation of therapy (Table 3).

DISCUSSION

The study indicates the efficacy and the safety of a 6-week course of flutamide as a tumor volume reducing agent in advanced JNA. Significant tumor regression was recorded in the postpubertal patients, whereas prepubertal patients demonstrated minimal response, and even tumor progression. The postpubertal patients had a mean tumor regression of 16.5%. No postpubertal patient had significant tumor progression while on flutamide therapy and maximal regression noted was up to 40%. Symptomatic improvement was noted, as was functional improvement in patients with functional deficits consequent to optic nerve compression. No significant side effects, other than transient breast tenderness, were noted.

Spontaneous regression of tumor size in JNA has been described but is unusual[19,20] and, when noted, is extremely slow, occurring over many years.[19,21,22] Reports indicate that the tumor may decrease in aggressiveness as it enters the third decade.[23] The decrease in tumor size as noted in this study cannot be reasonably ascribed to spontaneous regression for the reasons that it was much more marked and rapid than is the case with spontaneous regression and, further, that the response was restricted to the postpubertal group, and the degree of response correlated significantly with the patients' pretherapeutic testosterone levels ($p < .05$; Figure 3).

The other objective sign of tumor regression as noted in this study (ie, visual improvement) may also not be attributed to spontaneous improvement. The scant literature that exists on visual loss in JNA

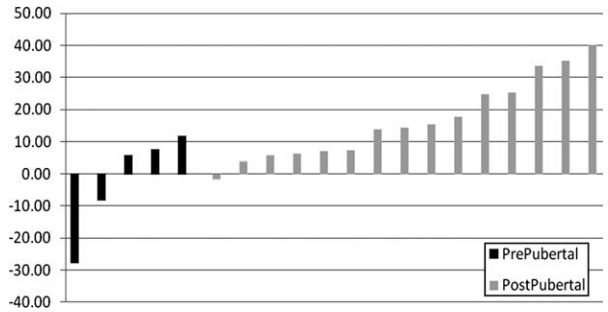

FIGURE 2. Waterfall plot demonstrating changes in tumor volume following flutamide therapy in prepubertal and postpubertal cases. Changes in tumor volume listed incrementally for the prepubertal and the postpubertal groups.

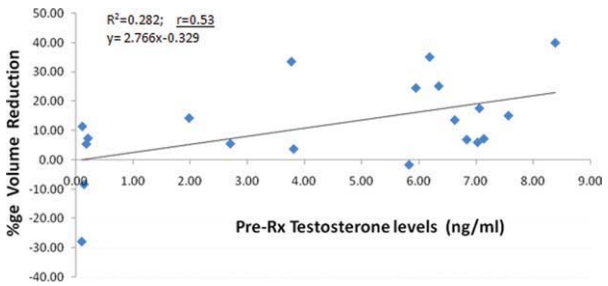

FIGURE 3. Scatter diagram demonstrating the correlation between serum testosterone level and tumor volume reduction. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

indicates it to be secondary to nerve compression,[24] and indicates that spontaneous improvement is not to be expected.[23]

Two previous reports,[14,15] with a total of 11 patients, have assessed flutamide in JNA. This study of 20 cases supplements the 2 previous studies but has included a more precise volume-measuring technique (gadolinium enhanced MRI rather than CT),[19] and also the blinding of volume measurements as being pretherapy or posttherapy. Further, testosterone levels and their change with therapy have been measured. The increase in serum testosterone levels with flutamide therapy indicates the effectiveness of the receptor blockade. The correlation between the treatment response and the pretherapy testosterone levels ($r = .53$, $p < .05$) indicates tumor responses being consequent to such testosterone receptor blockade, and strongly supports the initial presumption of testosterone stimulation being one of the significant factors responsible for tumor growth in JNA. The lack of significant responses in the prepubertal cases with low testosterone levels further confirms the thesis that significant clinical responses may be expected only in patients with higher testosterone levels.

The difference in the response to flutamide in the 2 previous studies may relate to differences in the treatment duration. The first report by Gates et al[14] included 5 patients and noted tumor regression of up to 62% (mean, 29%) as measured by CT scanning after 6 weeks of flutamide (500 mg/day in divided doses). Four of 5 patients had tumor regression, and 1 patient had tumor enlargement while on therapy. All tumors were relatively small (Chandler stage I–II; ie, restricted to nasopharynx, nose, and sphenoid sinus; mean tumor volume, 56.5 cm^3; range, 7.7–95.9 cm^3), and evaluation of their patient data as reported suggests all patients to be postpubertal. The other report by Labra et al[15] included only larger tumors (Chandler stage IV; ie, intracranial extension; mean tumor volume, 218.8 cm^3; range, 187.2–243.8 cm^3), and evaluation of their patient data as reported indicates 6 of 7 patients were postpubertal, and 1 other patient as possibly prepubertal (11 years, male). They administered flutamide for 3 weeks in a similar dosage, and used similar measurement techniques with CT imaging. All patients had tumor regression, but the degree of response noted was considerably less (mean, 7.2%; range, 4.8–11.1%).

Summarizing the patient data of the 2 reports in the literature and the present study, the 6-week treatment course seems more efficacious (mean tumor regression of 29%[14] and 16.5%; present study) than treatment for 3 weeks (mean tumor regression, 7.2%[15]). It is possible that prolonged therapy of duration >6 weeks may further enhance response, and such long-term use could find potential application in the control of small recurrent tumors, or tumors with significant intracranial extension. Flutamide has been used for long-term treatment continuing for months in adults with metastatic prostatic cancer. Experience with long-term use for 12 months in adolescents has demonstrated that the induced androgen blockade does not interfere with bone mineral density,[25] but the impact, if any, on sexual maturation of adolescent males has not been elucidated. Androgen blockade by flutamide in the doses as administered (10 mg/kg) is not complete,[26,27] and the experience with 6 weeks of treatment as noted in this study does indicate that clinically manifest derangements of sexual characteristics were occasional and minimal (transient breast tenderness), and reversible on cessation of treatment. No permanent effects of such partial and short-term androgen blockade were noted on evaluation of sexual maturation at 6 months' follow-up. Further prolongation of treatment beyond the experience in this study, however, would need to be undertaken with caution and under close observation, but may be appropriate when alternate treatment strategies of surgical excision or radiation therapy too are not entirely risk free.

This study was restricted to patients with advanced-stage JNA, although previous studies have reported good tumor regression in smaller tumors with a similar 6-week course of flutamide.[14] On current evidence, treatment responses may be expected in postpubertal cases of JNA. The degree of volume reduction, however, has been variable, and this variation can only be partly attributed to the variation in serum testosterone levels ($R^2 = 0.28$). Other factors that also may have a role remain to be elucidated.

The clinical impact of tumor regression is clearly manifest in patients with significant tumor regression, but the clinical import of more modest tumor responses is difficult to judge and has been questioned in the literature.[15] However, we would not undermine the clinical benefit that is achieved with lesser degrees of tumor regression. The advantages offered by such regression could include the following. First, the regression of the tumor along its periphery may facilitate surgical delineation of the tumor from the surrounding normal tissue, and ease tumor excision. Second, the major surgical morbidity in JNA is consequent to the tumor being in direct apposition to, or causing compression of, vital structures such as the dura, the optic nerve, and the cavernous sinus. Tumor regression can limit such morbidity and ease separation of tumor from these structures. Third, regression in tumor size may allow for a more conservative surgical approach. This may lead to the avoidance of a craniotomy in larger tumors, or the avoidance of a facial incision in smaller tumors. Fourth, the regression of this lobulated tumor from its foraminal and other extensions may facilitate a more complete removal and possibly lead to fewer recurrences. Fifth, flutamide-induced tumor regression may lead to decreased blood loss and a corresponding decrease in surgical morbidity. This particular study has not looked at the impact of flutamide on tumor vascularity and surgical blood loss, primarily because of

the multiple confounding factors affecting surgical blood loss and the difficulty of ascribing any changes to a single factor. The literature, however, does note the association between surgical blood loss and JNA tumor size,[28] and also that hormonal treatment with estrogen leads to histological maturation of the vascular endothelium in JNA.[1]

In conclusion, this study has demonstrated the safety and the beneficial impact of a 6-week course of flutamide on JNA and further clarified that the degree of tumor regression is correlated with serum testosterone levels and is mainly limited to patients that have attained puberty. Presurgical adjuvant treatment with flutamide can facilitate surgical excision and limit surgical morbidity. The demonstration of such clinical response also opens up for investigation the possible role for flutamide and other hormonal agents in the treatment of postexcision residual intracranial and extracranial tumors.

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