Successful Antiangiogenic Therapy of Giant Cell Angioblastoma With Interferon Alfa 2b: Report of 2 Cases

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ABSTRACT. We describe 2 cases of angioblastoma, a rare, destructive pediatric tumor, treated with interferon alfa 2b (IFNα2b). The first patient is a 10-month-old male who presented with an ulcerated palatal neoplasm that could not be completely resected. The second is a male neonate with a congenital tumor of the right hand that invaded the hypopharinx, destroying the fourth and fifth metacarpals. Biopsy in both patients was interpreted as giant cell angioblastoma. Angioblastoma is rare; there is only 1 reported case that necessitated amputation of an upper extremity, also initially recommended for our patient. Because there is little experience with chemotherapy, permission was granted to employ an antiangiogenic regimen of IFNα2b. The angiogenic protein, basic fibroblast growth factor (bFGF), was abnormally elevated in both patients.

Both patients received IFNα2b. In the first child, it was used after incomplete resection, because biopsy-proven tumor was present at the margin and in the nasopharynx. Biopsies 15 months after initiation of IFNα2b were negative for tumor. Therapy was stopped after 3½ years. Eighteen months later, the patient remains disease-free. In the second child, IFNα2b was started after debridement of the ulcerated tumor. Over 11 months, the tumor completely regressed and there was bony regeneration of the metacarpals. The fifth digit was amputated because of damage to the metacarpophalangeal joint by the tumor. IFNα2b therapy was discontinued after 1 year of treatment, and the child remains disease-free 2 years and 8 months later.

In conclusion, this report demonstrates that: 1) a bFGF-overexpressing low-grade tumor can respond to IFNα2b in a manner similar to life-threatening infantile hemangiomas, 2) urinary bFGF levels can help guide IFNα dosage in such patients, and 3) although bFGF-mediated tumor angiogenesis is inhibited by IFNα, physiologic angiogenesis seems to be unaffected. Pediatrics 2002; 109(2). URL: http://www.pediatrics.org/cgi/content/full/109/2/e37; interferon alfa 2b, giant cell angioblastoma, angiogenesis, basic fibroblast growth factor.

ABBREVIATIONS. IFNα, interferon alpha; bFGF, basic fibroblast growth factor; sc, subcutaneous; SGOT, serum glutamic oxaloacetic transaminase; MRI, magnetic resonance imaging.

The field of angiogenesis research began in 1971 with the hypothesis that tumor growth is angiogenesis-dependent.1 Angiogenesis mediates the fundamental processes of reproduction, development, and repair. An orderly, precise physiologic sequence of events tightly controls the normal growth of blood vessels. However, in pathologic situations, angiogenesis can proceed unabated, sustaining the progression of neoplastic or nonneoplastic disease.2,3 Angiogenesis inhibitors suppress the unregulated growth of blood vessels and may have a clinical role in such disorders.4

Giant cell angioblastoma is a rare neonatal tumor. Only 1 case has been reported in the literature—an upper extremity tumor in a female infant that required amputation of the arm.5 Resection was a daunting alternative in our 2 patients. Clear surgical margins of the maxilla and nasopharynx could not be achieved in the first child, and a surgical cure in the second child would have required amputation of the hand.

Interferon alfa (IFNα), a naturally occurring protein synthesized by leukocytes, has both antitumor6 and antiangiogenic properties.7 As a recombinant protein, it is one of few approved drugs that is also an angiogenesis inhibitor. The decision to use IFNα (Schering-Plough, Kenilworth, NJ) in these children was based on the following rationale: 1) We previously reported that proliferative phase hemangiomas overexpress basic fibroblast growth factor, a potent angiogenic protein,8 2) basic fibroblast growth factor (bFGF) is abnormally elevated in the urine of infants with growing hemangiomas9 and was found to be elevated in the children reported here, 3) IFNα inhibits overproduction of bFGF by human tumor cells,10 4) IFNα can regress life-threatening steroid-resistant hemangiomas10–22 and 5) a large giant cell tumor of the mandible in a 5-year-old child, which recurred 3 times after surgical resection, completely regressed with IFNα therapy.23

CASE REPORTS

Case 1

The patient was the product of a full-term uncomplicated pregnancy. At 3 months of age, he began to have trouble feeding and his father, an anesthesiologist, noted mid-palatal discoloration, initially localized to the hard palate. Thereafter, ulceration appeared and extended to involve both the hard and soft palate. A
biopsy done at 10 months of age revealed giant cell angioblastoma, and he was referred to Children’s Hospital (Fig 1). His urinary bFGF was 100,789 pg/g creatinine (normal: <4000 pg/g creatinine; Fig 2).

When the patient was 11 months old, resection of the hard and soft palate was done, leaving a rim of posterior palatal tissue, including the uvula. Pathologic examination confirmed the diagnosis, but there were positive margins at the lateral edge of the hard palate, vomer, and at the anterior edge of the soft palate. Another resection was done 6 days later, again with positive margins, as well as tumor in the nasopharynx by biopsy. After these resections, urinary bFGF decreased from 100,789 to 19,505 pg/g creatinine. The value of 19,505 was taken 2 weeks after surgery and indicated the presence of residual tumor.

Given the extension of the tumor, a curative margin could not be achieved. The patient was started on IFN2b therapy at 14 months of age; the initial dose was 3 million IU (MIU)/m² subcutaneous (sc) daily. Serum glutamic oxaloacetic transaminase (SGOT) was normal before initiation of therapy (32 [normal range: 2–40]). Additional biopsies in the nasopharynx, done 1 month later because of rising urinary bFGF (42733 pg/g creatinine), were again positive. Biopsies of the maxilla, nasopharynx, posterior ethmoidal plate, and adenoids, at 18 months of age, were suspicious for residual giant cell angioblastoma in the perpendicular plate region. Subsequent biopsies of the adenoidal area at 2 years and 5 months of age were negative for tumor. Throughout this period, the patient received 3 MIU/m² IFN2b sc daily with no evidence of toxicity. His liver transaminases were slightly elevated during the period of therapy (SGOT 61 [normal range: 2–40], serum glutamic pyruvic transaminase 90 [normal range: 3–30] at 3½ years of age).

After 3½ years of therapy, there was no evidence of disease and the IFN2b was reduced to 1.8 MIU/m² sc every other day. Six months later, after a period of 4 years, the IFN2b was discontinued. At the time of this writing, the child is 6 years of age and has been off therapy for 18 months. His urinary bFGF levels have remained in the normal range (<4000 pg/g creatinine), except for a transient elevation that corresponded to a period of palatal ulceration caused by an obturating appliance.

Case 2

A male neonate, the full-term product of an uncomplicated pregnancy, was born with a violaceous mass involving the dorsal hypothenar eminence of his right hand. During the first few weeks of life, blistering progressed to formation of a moist eschar that separated exposing an ulcer.

Plain radiographs of the extremity revealed erosion of the 2 lateral metacarpals with narrowing of the fourth metacarpal and erosion of the fifth metacarpal (Fig 3). Magnetic resonance imaging (MRI) showed a soft tissue mass with ill-defined borders, measuring 1 × 1.5 × 3.3 cm, which enhanced on T2-weighted spin echo sequences suggesting a vascular nature. Computed tomography scans of the abdomen and chest were normal with no evidence of metastatic disease. A Doppler examination of the extremity demonstrated intact radial and ulnar arteries and superficial palmar arch.

The ulcerated tumor was partially excised, and the wound was covered with a split-thickness skin graft. Biopsy revealed giant cell angioblastoma involving skin and bone with focal epidermal necrosis. Urinary bFGF was 65,080 pg/g creatinine (normal: <4000 pg/g); urinary vascular endothelial growth factor was 507 pg/mL (normal: <300 pg/mL).

At 4 months old, the patient was started on IFNα2b, 3 MIU/m² sc daily. After 6 days of therapy, the patient’s SGOT rose to 274 (normal range for infant <1 year: 10–65) and IFNα2b was stopped. Over the next few weeks, the SGOT decreased to 73 and the medication was resumed at 50% of the initial dose. During the subsequent 6 weeks, liver function tests were unchanged and the initially prescribed dose was gradually reinstituted. After an additional rise in SGOT, however, the dose was readjusted to 75% of the original dose (2.25 million IU/m² sc daily) for the duration of therapy.

After 4 months of IFNα2b treatment, the ulcer over the hypothenar eminence healed, and there was radiographic evidence of bony regeneration of the fourth and fifth metacarpals (Fig 3). MRI documented slow shrinkage of the mass and, at 11 months, there was complete regression. Urinary bFGF fell dramatically and remained in the normal range (Fig 4). The child grew normally and passed neurodevelopmental milestones at the appropriate times.

Although there was bony regeneration of the metacarpal, the fifth digit functioned poorly because the ulcerated tumor had interfered with normal joint development. The digit remained in a position of lateral extension and could not be flexed; hand function was otherwise normal. Therefore, after 11 months of IFNα2b therapy, the child had a fifth ray resection. The patient remained on therapy, and there was normal healing of the amputation site (Fig 5). One month after the procedure, IFNα2b was discontinued. He received a total of 1 year of therapy. Two years and 8 months later, he remains well with no evidence of tumor either clinically or by MRI examination.

DISCUSSION

We present 2 infants with a rare, destructive vascular neoplasm treated with IFNα2b. The rationale...
for using IFNα2b therapy was based on laboratory and clinical findings that have evolved over the past decade.

Hemangiomas, characterized by disordered endothelial proliferation, are the most common tumor of infancy and occur in up to 10% of white children. The natural history of hemangiomas is comprised of an initial proliferative phase, marked by rapid growth (generally up to 1 year), followed by a slow involuting phase (from 1–8 years), and a final involuted phase. Although most cutaneous hemangiomas are small and harmless, approximately 20% cause endangering complications, such as visual or airway obstruction or ulceration/distortion or destruction of tissue. A subset of these hemangiomas are life-threatening, causing, for example, high-output cardiac failure secondary to shunting of blood through hepatic lesions. Systemic corticosteroid therapy remains the first choice for these endangering hemangiomas. The response of life-threatening hemangiomas to

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**Fig 2.** Urinary bFGF levels for patient 1 during the course of IFNα2b therapy (determined by enzyme-linked immunoabsorbent assay, R & D Systems, Minneapolis, MN).

**Fig 3.** Macroscopic and radiographic views of right hand of patient 2 during course of treatment. A, initial presentation with erythematous discoloration and ulceration over hypothenar eminence and bony loss involving fourth and fifth metacarpals. B, appearance after 6 doses of IFNα2b. C, after 4 months of therapy, there is evidence of healing and bony regeneration. D, continued improvement after 8 months of treatment. E, Final appearance of hand after fifth ray resection.
corticosteroids varies; 30% of patients have an excellent response, with 40% demonstrating stabilization (an equivocal response), and 30% failing to respond at all.25

Beginning in 1980, laboratory findings demonstrated that IFNα has antiangiogenic effects. It was discovered that interferon inhibits endothelial cell motility in vitro26 and that both IFNα and IFN-β can inhibit tumor-induced angiogenesis in murine animal models.27,28 This led to the first successful application of IFNα2a based on its antiangiogenic activity in a 7-year-old boy with diffuse pulmonary hemangiomatosis; this was the first demonstration of antiangiogenic therapy in humans.11,22 There was dramatic regression of the proliferative vascular lesions with symptomatic relief after treatment with 3 million IU/m2/day. This was followed by single and multiple case reports that validated the efficacy of IFNα for endangering or life-threatening infantile hemangiomas.11–22 IFNα2a and IFNα2b are equally efficacious forms of leukocyte IFNα that are distinguished numerically because they are manufactured by different pharmaceutical companies. Therapy with IFNα is now widely used for life-threatening hemangiomas that are corticosteroid-resistant and for the more aggressive Kaposiform hemangioendothelioma, a vascular tumor which is associated with profound thrombocytopenia.7,30,31

IFNα has diverse effects on neoplasms, both antitumor and antiangiogenic. Traditionally, in attempt to kill tumor cells, it has been used at very high doses (up to 20 MIU/m2 daily intravenously for 1 month), in an attempt to kill tumor cells.32,33 Antitumor effects include direct actions on cells—antiproliferative activity, cytostatic activity, enhancement of antigen expression—and indirect mechanisms—activation of macrophage, lymphocyte and natural killer cell cytocidal activity, cytokine induction, and modulation of antibody production.34 In contrast, antiangiogenic activity is optimum at low doses (≤3 MIU daily). Antiangiogenic actions of IFNα and β include downregulation of bFGF gene expression and protein production by tumor cells in vitro.9 In vivo experiments demonstrate that the systemic administration of IFNα inhibits the expression of bFGF by human bladder carcinomas growing in nude mice in association with angiogenesis inhibition.35

Basic fibroblast growth factor is a potent angiogenic protein. Abnormally high levels are reported in the serum of 10% and in the urine of 37% of cancer patients,26 and in wounds as well as in the urine of children with hemangiomas.7 From these results, we proposed that there may be a subset of patients with neoplastic and nonneoplastic disorders who have “diseases of bFGF overexpression.”44 Angiogenesis inhibitors may be helpful in patients who have angiogenesis-dependent disease.

In these patients, we used urinary bFGF to ascertain an ongoing physiologic response to IFNα. In children receiving IFNα for life-threatening hemangiomas or for other malignancies, our clinical experience has been that urinary bFGF typically decreases within weeks of initiating therapy at 3 MIU/m2. If the bFGF remains elevated, we increase the dose to 6 MIU/m2, as we have described previously.23 Urinary bFGF may be transiently elevated by injury secondary to trauma or surgery; however, such increases typically persist on a time scale of less than two weeks. When a patient has an elevated level, the test is repeated over the next several weeks to determine if the increase is sustained. If the rise persists, careful clinical and radiologic examination is mandated to evaluate the possibility of disease progression. There are no general principles at the current time regarding the duration of therapy with IFNα or with other angiogenesis inhibitors.

We generally do not alter dosage on the basis of neutropenia, which is likely secondary to “margination” of leukocytes against blood vessel walls rather than a result of bone marrow suppression. These patients were monitored closely for neurologic development, which remained normal in both patients. One of the few indications for discontinuing IFN is the development of spastic diparesis (increased muscle tone of the lower extremities with extensor plantar responses and delayed walking). Spastic diparesis has been reported in some children receiving IFN.
This generally occurs in infants <6 months of age. 38–41

We did not see the development of drug resistance in these 2 patients, nor in the other patients whom we have treated with IFNα.13,23 This may be attributable, in part, to the failure of this low-grade tumor to produce angiogenic factors other than bFGF, the target of IFNα.

It is also noteworthy that these patients grew normally, healed wounds after operations, and regenerated bone while on IFNα therapy. This suggests that physiologic angiogenesis proceeds normally while the patient is receiving IFNα. Thus, some angiogenesis inhibitors may selectively target pathologic angiogenesis, while sparing physiologic angiogenesis that mediates growth, reproduction, and repair.

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