Phase I trial of pegylated interferon- α -2b in young patients with plexiform neurofibromas

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ABSTRACT

Objective: Interferon has antiproliferative and antiangiogenic properties. We sought to evaluate preliminary efficacy and determine the recommended phase II dose (RP2D) for pegylated interferon- α -2b (PI) in patients with unresectable progressive or symptomatic plexiform neurofibromas (PN).

Methods: PI was administered weekly in cohorts of 3–6 patients during the dose-finding phase and continued for up to 2 years. Twelve patients were treated at the RP2D to further evaluate toxicity and activity.

Results: Thirty patients (median age 9.3 years, range 1.9–34.7 years) were enrolled. No dose-limiting toxicity (DLT) was seen in patients treated at the 3 μ g/kg dose level (DL) during the first 4 weeks. All 5 patients treated at the 4.5 μ g/kg DL came off study or required dose reductions for behavioral toxicity or fatigue. Similar DLT on the 3 μ g/kg DL became apparent over time. There was 1 DLT (myoclonus) in 12 patients enrolled at the 1.0 μ g/kg DL. Eleven of 16 patients with pain showed improvement and 13 of 14 patients with a palpable mass had a decrease in size. Five of 17 patients (29%) who underwent volumetric analysis had a 15%–22% decrease in volume. Three of 4 patients with documented radiographic progression prior to enrollment showed stabilization or shrinkage.

Conclusions: The RP2D of PI for pediatric patients with PN is 1 μ g/kg/wk. Clinical and radiographic improvement and cessation of growth can occur.

Classification of evidence: This study provides Class III evidence that pegylated interferon- α -2b in patients with unresectable, progressive, symptomatic, or life-threatening PNs results in radiographic reduction or stabilization of PN size. *Neurology*® 2011;76:265–272

GLOSSARY

AUC = area under the curve; **DL** = dose level; **DLT** = dose-limiting toxicity; **FDA** = Food and Drug Administration; **IFN** = interferon; **MTD** = maximum tolerated dose; **NF1** = neurofibromatosis type 1; **NHT** = nonhematologic toxicity; **PEG** = polyethylene glycol; **PI** = pegylated interferon- α -2b; **PN** = plexiform neurofibroma; **RP2D** = recommended phase II dose; **STIR** = short T1-inversion recovery; **TSH** = thyroid-stimulating hormone; **VA** = volumetric analyses.

Neurofibromatosis type 1 (NF1) is a common autosomal dominant neurogenetic disorder characterized by a wide variety of progressive cutaneous, neurologic, skeletal, and neoplastic manifestations.¹ PN are one of several types of neurofibromas that may occur in patients with NF1 and are characterized by a proliferation of Schwann cells, fibroblasts, and mast cells occurring along the length of a nerve. They occur in 25%–50% of adults and children with NF1,^{2,3} and typically infiltrate adjacent normal tissue, making complete surgical resection usually impossible. As they grow, they frequently become disfiguring as well as disabling or even life-threatening.^{4,5} Regrowth following subtotal resection is common.⁶ Standard chemotherapy is not effective and there is currently no standard medical treatment despite various clinical trials.^{7–9}

Interferons (IFNs) have both antiproliferative and antiangiogenic properties.¹⁰ A previous study evaluating daily injections of IFN- α -2a in patients with PN showed a high rate of

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prolonged stable disease as well as clinical improvement in approximately 20%.⁹ Conjugating proteins with polyethylene glycol (PEG) almost invariably lengthens the plasma half-life by reducing sensitivity to proteolysis, thereby increasing the area under the curve (AUC) and providing protracted activity.¹¹ Pegylation of IFN enhances the therapeutic ratio in patients with hepatitis C,¹² and PI has received Food and Drug Administration (FDA) approval for this indication at a dose of 1 $\mu\text{g/kg/wk}$.

We sought to determine the RP2D, evaluate the toxicity profile, and obtain preliminary activity data for PI given as a weekly injection to patients with PN.

METHODS **Standard protocol approvals, registrations, and patient consents.** Institutional review boards at participating institutions approved the study. Written informed consent was obtained from patients aged ≥ 18 years or from parents/legal guardians of children aged < 18 years, with child assent when appropriate according to individual institutional policies. The trial was registered with www.ClinicalTrials.gov identification number NCT00253474.

Eligibility. Patients ≥ 18 months of age with unresectable progressive, symptomatic, or life-threatening PN were eligible. Initially there was no upper age limit, but the study was amended to limit enrollment to patients < 21 years after untoward toxicity was encountered in adult patients enrolled on dose levels (DL) 1 and 2. Patients who met the diagnostic criteria for NF1 as defined by the NIH Consensus Conference¹³ were not required to have biopsy proof of a PN. Evidence of radiographic progression was not necessary. Patients had to have recovered from all toxic effects of previous therapy for their PN, a life expectancy of at least 12 months, and an Eastern Cooperative Oncology Group performance score of 0, 1, or 2. Adequate bone marrow (absolute neutrophil count $\geq 1,500/\mu\text{L}$, Hb > 10 g/dL, platelet count $\geq 100,000/\mu\text{L}$), renal (normal serum creatinine for age or a creatinine clearance ≥ 70 mL/min/1.73 m²), and hepatic (total bilirubin $< 1.5 \times$ normal and serum glutamic pyruvic transaminase $< 2 \times$ upper limit of normal) function was required. Baseline studies had to be obtained within 28 days of study entry.

Exclusion criteria included any clinically significant unrelated systemic illness, cardiovascular disease, or severe psychiatric condition, pregnancy or lactation, exposure to an investigational chemotherapy agent within 30 days, a visual pathway glioma requiring treatment with chemotherapy, or a history of any malignancy.

Study design. PI was administered as a weekly subcutaneous injection for up to 2 years unless there was evidence of disease progression, unacceptable toxicity, or the patient or parent requested to discontinue therapy. Patients or parents were taught to administer the medication in the outpatient setting. Acetaminophen (15 mg/kg up to maximum dose of 1,000 mg) was given 30 minutes prior to the first dose of PI and then every 4–6 hours as needed.

The initial starting dose of PI was 3.0 $\mu\text{g/kg/wk}$, with subsequent escalation to 4.5 $\mu\text{g/kg/wk}$. If one of the first 3 patients treated at any DL experienced DLT during the first 4 weeks of treatment, up to 3 additional patients were treated at that DL; if no DLT was observed during that time, the dose would be escalated. The maximum tolerated dose (MTD) was defined as the DL immediately below that at which 2 or more patients in a cohort of up to 6 experienced DLT. Due to the observation of delayed toxicity at the first 2 DLs, the study was redesigned and amended to exclude patients > 21 years old, extend the evaluation period to 8 weeks in a cohort of 12 patients, and de-escalate the dose to 1.0 $\mu\text{g/kg}$, the FDA-approved dose for the treatment of hepatitis C. If more than 2 of 12 patients developed DLT, the DL was to be de-escalated further to DL -1 (0.6 $\mu\text{g/kg/dose}$), and if necessary to 0.4 $\mu\text{g/kg/week}$. The RP2D was therefore defined as the level where 2 or fewer out of 12 patients developed DLT.

Toxicities were graded according to NCI Common Toxicity Criteria (CTC version 2.0). DLT was initially defined as grade 4 neutropenia or thrombocytopenia that persisted for ≥ 7 days and grade 3 or 4 nonhematologic toxicity (NHT) attributable to PI (excluding nausea and vomiting, infection, fever, or grade 3 hepatic toxicity that returned to grade 1 or less within 2 weeks of discontinuing PI). At the time, the DLT observation period was extended to include the first 8 weeks of treatment, the definition of DLT was amended to include intolerable behavioral/mood changes, such as hyperactivity, aggression, irritability, or depression that required dose reduction or discontinuation, and persistent (i.e., not transiently related to the injection) grade 2 or higher intolerable constitutional symptoms.

Toxicity evaluations and dose modifications. Patients were seen at weeks 2, 4, 8, and 12, then at months 4, 12, 18, and 24. Toxicity and clinical response to treatment, complete blood counts, and chemistries with liver function tests were evaluated at each visit. Patients who developed grade 4 NHT, grade 3 hyperbilirubinemia, or grade 2 or higher cardiopulmonary toxicity were to be taken off study. Patients with any other DLT had the drug held until toxicity resolved to grade 1 or better, at which point the drug could be restarted at the next lower DL.

Response evaluation. MRI scans were performed at baseline and after cycles 3, 7, 12, 18, and 24 while on treatment. Initially, WHO solid tumor response criteria based on 2-dimensional tumor measurements were used to assess response. At the time the study was amended to treat patients at the 1.0 $\mu\text{g/kg}$ DL, short T1-inversion recovery (STIR) imaging was required with each MRI scan so that volumetric analyses (VA) could be performed to allow for more sensitive measurement of changes in PN size. A detailed history and physical and patient/parent questionnaire at the time of each response evaluation was used to evaluate clinical response, including improvement in pain, decreased need for pain medications, and subjective decrease in visible mass.

Volumetric MRI method. Axial and coronal STIR MRI were obtained to encompass the entire PNF using a slice thickness of 5–10 mm with no skips between slices. PN volume was determined as previously described using the MEDx software platform.¹⁴

RESULTS Thirty patients (median age 9.3 years, range 1.9–34.7 years) were enrolled between November 2001 and January 2006. All but one patient with a biopsy-proven PN met the clinical criteria for

Table 1 Baseline patient characteristics

No.	Age, y	Sex	Dose level	Previous treatment	Location	Symptoms
1	14.5	F	1	Surgery	Neck/cervical spine	Palpable mass
2	7.5	F	1	Multiple surgeries; cis-retinoic acid; interferon	Orbit	Headaches
3	23.1	F	1	Surgery	Spine	Back pain
4	27.0	M	1	Surgery, thalidomide, cis-retinoic acid	Spine	Quadriparesis
5	11.7	F	1	Surgery	Spine and chest wall	Leg weakness; paresthesias
6	17.2	F	1	Multiple surgeries	Left neck and face	Palpable mass
7	3.8	M	1	Surgery	Orbit	Proptosis
8	34.6	M	2	Surgery	Cervical spine	Quadriparesis, paresthesias
9	23.0	M	2	3 prior surgeries; oral VP-16	Cervical spine	Quadriparesis and lower extremity spasms
10	7.7	M	2	Surgery	Left neck, mediastinum	Palpable mass
11	8.9	M	2	None	Lumbar spine	None
12	2.2	F	2	Surgery	Left orbit, cavernous sinus	Proptosis
13	1.8	F	1	None	Chest, mediastinum, neck, brachial plexus, retro-peritoneum	Quadriparesis; back and neck pain
14	6.1	M	1	Surgery	Left shoulder, skull base, brachial plexus, neck	Palpable mass; chest/neck/shoulder pain
15	3.9	F	1	Surgery	Left orbit, forehead, scalp	Proptosis
16	12.9	M	1	None	Left brachial plexus	Palpable mass; shoulder pain
17	9.4	F	1	None	Occipital scalp	Palpable mass; scalp pain
18	6.5	F	1	None	Retroperitoneum left leg	Palpable mass
19	5.3	M	0	Surgery; methotrexate/Velban; pirfenidone; thalidomide	Neck, shoulder	Palpable mass; neck/shoulder pain
20	6.4	M	0	Surgery; tipifarnib; thalidomide; pirfenidone	Left face, orbit	Headaches; proptosis
21	1.9	F	0	Surgery	Pelvis, paraspinal, legs	Weakness; back pain
22	7.5	M	0	Surgery, thalidomide; pirfenidone	Abdomen; pelvis, lower extremities	Leg pain; paresthesias, leg weakness
23	9.0	M	0	Surgery	Left shoulder	Palpable mass; shoulder pain
24	11.9	M	0	Surgery; tipifarnib	Left orbit, skull, cavernous sinus	Proptosis
25	14.3	M	0	Surgery	Spine, brachial plexus, mediastinum	None
26	12.3	F	0	None	Left brachial plexus, neck	Arm weakness
27	10.7	M	0	Surgery; tipifarnib; pirfenidone	Pelvis, thigh	Sacral pain; weakness
28	14.5	M	0	Pirfenidone	Pelvis	Diarrhea, urinary urgency
29	15.6	F	0	Surgery	Pelvis	None
30	4.0	M	0	Surgery	Paraspinal, retroperitoneum	Bilateral leg pain

NF1.¹ Twenty-four patients had previously undergone surgical debulking or other medical treatment for their PN (table 1).

Toxicity. *Dose level 1 (3.0 µg/kg).* Thirteen patients were enrolled, of whom 11 were evaluable for toxicity (table 2). One patient received a lower dose (1 µg/kg) due to a calculation error, which was not discovered until he came off study for an unrelated adverse event, and one adult patient withdrew consent after 3 weeks of therapy. Two patients were taken off study for toxicity. A 23-year-old woman developed a

tonic-clonic seizure during week 13 of therapy. She was started on anticonvulsants and continued PI at a reduced dose but had a second seizure 4 weeks later. The PI was discontinued and she was removed from study and had no further seizures. A 3.8-year-old boy developed increasingly severe aggression, oppositional/defiant behavior, and hyperactivity, and was withdrawn from study after 15 months of treatment. Of the 9 remaining evaluable patients, 2 developed intolerable behavioral problems over time with hyperactivity, aggression, and oppositional/defiant

Table 2 PEG-intron toxicities requiring dose reductions

Dose level	Toxicity	Age, y	Grade	Week dose reduced or held
1 (3 µg/kg) (n = 11 evaluable)	Seizures	23.1	3	13
	Behavior	12.9	2	39
	Neutropenia	9.4	4	8
	Behavior	3.9	2	59
	Behavior	3.8	3	65
2 (4.5 µg/kg) (n = 5)	Behavior	2.2	3	28
	Fatigue	23	2	32
	Fatigue	8.9	3	73
	Myalgia/behavior	7.7	3	33
	Fatigue	34.6	2	48
3 (1 µg/kg) (n = 12)	Myoclonic jerks	11	3	1
	Elevated transaminases (ALT/AST)	12	3	24

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.

behavior, and a third patient developed dose-limiting neutropenia.

Dose level 2 (4.5 µg/kg). Five patients were enrolled. Two patients (age 25 and 34 years) developed intolerable fatigue and discontinued the drug after 6–8 months of therapy. Of the 3 younger patients, one developed severe behavioral problems and depression after 2–3 months of treatment as well as severe myalgias requiring dose reduction. Another patient developed increased hyperactivity and behavioral outbursts within weeks of starting therapy, which became intolerable and required dose reduction. The third patient required dose reduction for persistently

severe fatigue. All symptoms requiring dose reduction/withdrawal became intolerable after the evaluation period (4 weeks) was completed.

Dose level 0 (1.0 µg/kg). Twelve patients were enrolled. There was one DLT in a 10-year-old boy who developed myoclonic jerks of his upper and lower extremities shortly after receiving the first dose of PI. The PI was held and over the next 3 weeks, the myoclonus became less frequent and eventually resolved. The PI was restarted at a dose of 0.6 µg/kg/wk but the myoclonus recurred, this time resolving within a few days. The PI was restarted at 0.3 µg/kg/wk but the myoclonus again recurred, at which point the patient was taken off study. A few weeks later, the myoclonus occurred again and continued intermittently for months after discontinuing the drug. A second patient developed grade 3 elevation of SGPT and SGOT after 6 months of treatment. These returned to normal after the drug was discontinued but the toxicity recurred when the PI was restarted at 0.6 µg/kg/week. The toxicity resolved when the drug was held but the family decided to stop treatment. This dose level was therefore determined to be the RP2D.

Constitutional symptoms (fever, chills, fatigue) were almost universal after the first dose and were more severe and less likely to subside over time at the higher DLs. Non-dose-limiting toxicities at the RP2D (table 3) consisted mostly of mild constitutional symptoms and nausea/vomiting that occurred within hours of each dose and generally improved over the first few weeks. Three patients developed an elevated thyroid-stimulating hormone (TSH), with a normal free T₄. No treatment was required and the TSH returned to normal after therapy was completed. Mild grade 1 and 2 neutropenia was common. Three patients (25%) developed grade 3 neutropenia: in 2 patients the neutropenia occurred after several months of treatment and resolved to grade 1 or less despite continuing drug; 1 patient developed grade 3 neutropenia during the first month in conjunction with myoclonic jerks, with subsequent discontinuation of the drug.

Responses. Responses are summarized in table 4. Eleven of 16 patients (69%) with baseline pain had improvement or resolution of pain after starting treatment, although 2 patients with initial improvement eventually developed clinical worsening. Thirteen of 14 patients (93%) with a visible or palpable mass had a subjective decrease in size, and 4 of 5 patients with proptosis secondary to an orbital PN showed noticeable improvement in the ability to open the eye. Twelve patients did not have VA performed either because they did not have STIR images obtained or because of small tumor size or poor

Table 3 Non-dose-limiting toxicities related to protocol therapy and observed in more than 10% of patients at the RP2D (1 µg/kg) (n = 12)

Toxicity	Grade 1		Grade 2		Grade 3	
	No. patients	No. courses	No. patients	No. courses	No. patients	No. courses
ALT	5	9				
AST	3	5				
ANC/neutropenia	6	7	5	9	3	3
Fatigue	5	11				
Fever/chills	5	6	3	3		
Headache	3	3				
Leukopenia	7	9	4	4		
Nausea	4	6				
TSH (high)	3	3				
Vomiting	2	2				
Weight loss	4	4				

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; RP2D = recommended phase II dose; TSH = thyroid-stimulating hormone.

Table 4 Radiographic and clinical responses

No.	Dose level	Clinical response	Volumetric analysis	Time on study, mo	Reason off study
19	0	Decrease in size of mass; neck/shoulder pain improved	Stable disease in previously progressing patient	17	Unrelated adverse event
20	0	Decrease in size of orbital mass; headaches resolved, able to open eye	16% decrease	24	Completed therapy
21	0	No change	PD, 44% increase	11	PD
22	0	No change	PD, 25% increase	15	PD
23	0	Decreased size of shoulder mass; shoulder pain improved	SD, <10% change	24	Completed therapy
24	0	Decrease in size of orbital mass; able to open eye	SD, <10% change	24	Completed therapy
25	0	Asymptomatic	SD, <10% change	24	Completed therapy
26	0	No change	SD, 16% increase	9	Toxicity/parent request
27	0	No change		1	Toxicity
28	0	No change	17% decrease	24	Completed therapy
29	0	Asymptomatic	SD, <10% change	19	Parent request
30	0	Leg pain improved	9% decrease, then increase by 31% by end of therapy	24	Completed therapy; PD
1	1	Decreased size of neck mass	19% decrease	24	Completed therapy
2	1	Headaches improved	ND	24	Completed therapy
3	1	No change	ND	3	Toxicity
4	1	Not evaluable	Not evaluable	0.75	Withdrawal of consent
5	1	Chest wall mass increased secondary to malignant degeneration	ND	6	PD
6	1	Decreased size of facial mass	ND	24	Completed therapy
7	1	No change	ND	15	Toxicity
13	1	Increased leg and neck strength, improvement in pain initially followed by clinical worsening	ND	11	PD
14	1	Decreased size of mass; neck/chest pain improved	SD, <10% change	14	Unrelated adverse event
15	1	Decreased size of orbital mass; able to open eye	15% decrease	24	Completed therapy
16	1	Decreased size of mass; shoulder pain improved	6% decrease, then PD by 35% by end of therapy	24	Completed therapy; PD
17	1	Decreased size of scalp mass; scalp pain improved	ND	20	Noncompliance
18	1	Decreased size of leg mass	ND	24	Completed therapy
8	2	No change	ND	11	Toxicity
9	2	Improvement in slower extremity spasms	ND	8	Toxicity
10	2	Decreased size of neck mass	22% decrease	24	Completed therapy
11	2	Asymptomatic	SD, <10% change	24	Completed therapy
12	2	Decreased size of orbital mass; headaches improved; able to open eye	ND	24	Completed therapy

Abbreviations: ND = not done; PD = progressive disease; SD = stable disease.

contrast between the tumor and surrounding tissues. Seventeen patients had the necessary imaging performed at baseline and at some point during the study to be able to undergo VA of response. Five of these patients (29.4%) showed a 15%–22% decrease in the volume of their tumor during the course of

treatment. Due to inconsistencies in the imaging obtained, VA was not able to be obtained at each time point for all patients, so that determination of the median time to best response was not possible. However, responses seemed to be fairly rapid, with a 10%–18% decrease in volume by 4–6 months in the

Figure

Plexiform neurofibroma (PN) growth before, during (in red), and after treatment with pegylated interferon- α -2b (PI)

Patient 28: Pelvic PN volume prior to starting treatment, with a subsequent 17% decrease in size after starting PI, followed by an increase in volume after discontinuing treatment.

4 responding patients who had VA performed at the first time point. Responses tended to plateau or diminish after the first year. Of the 4 evaluable patients who had documented radiographic progression by VA prior to starting PI therapy, tumor volume stabilized or decreased in 3. All of these patients had developed progressive disease on various other therapeutic trials for PN. The figure shows the growth of a large pelvic tumor in patient 28 prior to, during, and following treatment with PI.

Five patients developed tumor progression 11–24 months after starting treatment, including 3 patients who showed initial clinical or radiographic improvement, or both. A sixth patient (no. 5) developed rapidly progressive disease after 6 months of treatment and was found to have malignant degeneration of a chest wall PN and died.

No patient had a >25% decrease in tumor size by 2D measurements.

DISCUSSION IFNs exert antitumor activity through direct antiproliferative and cytotoxic effects as well as modulation of the host immune response.¹⁰ IFN is also a potent inhibitor of angiogenesis as evidenced by its utility in the treatment of life-threatening hemangiomas of infancy.¹⁵ In tumor cell lines, continuous and prolonged exposure to IFN optimizes both the antiproliferative and antiangiogenic effect^{16–19} and the highest response rates in patients with metastatic melanoma have been obtained with

uninterrupted schedules.¹⁶ When IFN was removed from the medium, glioma cell line growth rapidly returned to the pretreatment rate.¹⁸

Although IFN- α has been used to treat a variety of neoplasms, the optimal dose has not been established. In vivo studies have not shown a clear dose-response relationship in solid tumors, other than for possibly melanoma.²⁰ In CML, low-dose IFN is as effective as higher doses,²¹ whereas toxicity is clearly dose-related. In a study of the optimal antiangiogenic dose and schedule of IFN- α -2a in a human bladder cancer cell line resistant to the antiproliferative effects of IFN implanted into the bladders of nude mice, doses far below the maximally tolerated dose produced the most significant inhibition of tumor growth, vascularization, and inhibition of angiogenesis-regulating genes.¹⁹ These effects were maximal when the IFN was given daily. Administration of higher doses failed to produce significant antiangiogenic effects. The optimal dose in this study correlates with a PI dose of 0.3–0.4 $\mu\text{g/kg/wk}$. Indeed, in our study, responses were seen at the lower DLs, supporting the preclinical data. Furthermore, dose de-escalation was required due to intolerable fatigue in older patients and behavioral changes in younger patients. These toxicities typically developed after several weeks, necessitating a longer observation period in order to adequately assess tolerability. This is consistent with the conclusions of an analysis of NF-1–related trials that the clinical trial design and endpoints used in patients with refractory cancer are not necessarily appropriate for patients with NF1-related tumors.⁵

The responsiveness of PN to IFN was first reported in 2006²² in a child with a PN of the pelvis causing severe pain due to nerve compression. The patient experienced dramatic pain relief within 2 weeks of starting IFN, although no objective decrease in the size of the tumor by standard imaging was seen. A randomized, noncomparative phase II trial treated 57 evaluable patients with unresectable PN with either cis-retinoic acid or IFN- α -2a.⁹ At 18 months of follow-up, 26 of 27 of patients (96%) treated with IFN were considered to be stable and 5 patients (18%) showed symptomatic improvement. Although the radiographic responses cannot be compared to the current trial given the different evaluation criteria, the percentage of patients who had improvement in pain and a subjective decrease in the size of the visible or palpable tumor seems better on our trial using the pegylated form of IFN.

A longitudinal study evaluating PN growth rate showed a significant variability among patients,²³ making clinical trial design for treatment of these tumors challenging. No study to date has demonstrated

significant radiographic responses using standard 2D response evaluation. This is most likely due to the innate resistance of the tumor to the therapeutic agents evaluated thus far. In addition, the infiltrating nature and large size of these tumors make 2D measurements, and therefore determination of change in size over time, imprecise. Since PN are bright compared with normal-surrounding tissue on STIR MRI, a program for automated volumetric analysis using STIR images that reproducibly quantifies the volume of these complex lesions and detects small changes over time was developed and validated at the National Cancer Institute.^{14,23} Using this technique, we found that approximately 30% of patients had a decrease in the volume of the tumor and an additional subset of patients with documented progression prior to starting the drug had a definite plateau in growth rate after starting PI. Since PN growth is often most rapid in younger children,²³ the ability to halt growth during the period when these tumors grow the fastest is of tremendous benefit. Furthermore, approximately 70% of patients with baseline pain showed subjective improvement within weeks of starting therapy, and the majority of patients with a visible or palpable mass had a subjective decrease in tumor size, including a noticeable improvement in proptosis and the ability to open the eye. We acknowledge the limitations of using subjective assessments to determine clinical response and more stringent, validated criteria have been incorporated into an ongoing phase II study. Mandated STIR images at baseline and with each scheduled evaluation will also allow us to better understand the time course of response and the optimal duration of therapy.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Douglas M. Potter.

DISCLOSURE

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Editor's Note to Authors and Readers: Levels of Evidence coming to *Neurology*®

Effective January 15, 2009, authors submitting Articles or Clinical/Scientific Notes to *Neurology*® that report on clinical therapeutic studies must state the study type, the primary research question(s), and the classification of level of evidence assigned to each question based on the classification scheme requirements shown below (left). While the authors will initially assign a level of evidence, the final level will be adjudicated by an independent team prior to publication. Ultimately, these levels can be translated into classes of recommendations for clinical care, as shown below (right). For more information, please access the articles and the editorial on the use of classification of levels of evidence published in *Neurology*.¹⁻³

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Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements.

Class IV. Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

AAN classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.