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Sirolimus for progressive neurofibromatosis type 1–associated plexiform neurofibromas: a Neurofibromatosis Clinical Trials Consortium phase II study

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Background. Plexiform neurofibromas (PNs) are benign peripheral nerve sheath tumors that arise in one-third of individuals with neurofibromatosis type 1 (NF1). They may cause significant disfigurement, compression of vital structures, neurologic dysfunction, and/or pain. Currently, the only effective management strategy is surgical resection. Converging evidence has demonstrated that the *NF1* tumor suppressor protein, neurofibromin, negatively regulates activity in the mammalian Target of Rapamycin pathway.

Methods. We employed a 2-strata clinical trial design. Stratum 1 included subjects with inoperable, NF1-associated progressive PN and sought to determine whether sirolimus safely and tolerably increases time to progression (TTP). Volumetric MRI analysis conducted at regular intervals was used to determine TTP relative to baseline imaging.

Results. The estimated median TTP of subjects receiving sirolimus was 15.4 months (95% CI:14.3–23.7 mo), which was significantly longer than 11.9 months ($P < .001$), the median TTP of the placebo arm of a previous PN clinical trial with similar eligibility criteria.

Conclusions. This study demonstrated that sirolimus prolongs TTP by almost 4 months in patients with NF1-associated progressive PN. Although the improvement in TTP is modest, given the lack of significant or frequent toxicity and the availability of few other treatment options, the use of sirolimus to slow the growth of progressive PN could be considered in select patients.

Keywords: neurofibromatosis, NF1, plexiform neurofibroma, rapamycin, sirolimus, mTOR.

Neurofibromatosis type 1 (NF1) is a common autosomal dominant disorder with an incidence of 1:3000 worldwide (>80 000 persons affected in the United States alone).[1] NF1 is caused by a germline mutation in the *NF1* tumor suppressor gene located on chromosome 17q11.2. Patients with NF1 have an increased risk of developing central and peripheral nervous system tumors, including plexiform neurofibromas (PNs).[2–4] PNs are benign peripheral nerve sheath tumors that arise in one-third of individuals with NF1. While they are usually diagnosed early in life, where they may be multiple in number, PNs can grow throughout the lifetime of the individual.[4–8] Despite their benign histology, these tumors may cause significant disfigurement, compression of vital structures, neurologic dysfunction, and/or pain,[5,9,10] which can negatively impact quality of life (QoL).[11,12] Moreover, some PNs can transform into malignant peripheral nerve sheath tumors (MPNSTs), a highly aggressive and metastatic cancer.[13] Currently, the only effective management strategy available for PNs is surgical resection.

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Converging evidence has demonstrated that the *NF1* tumor suppressor protein, neurofibromin, controls cell growth by negatively regulating mammalian Target of Rapamycin (mTOR) pathway activity.[14,15] Mammalian TOR functions as a central integrator of many key cellular functions, including cell size/growth, proliferation through modulation of cell proliferation, protein translation, angiogenesis, and cell survival.[16,17] Moreover, mTOR pathway activation underlies tumor proliferation in *NF1* genetically engineered mouse models and human NF1-associated tumor explants.[14,18–20] Based on these preclinical findings, we targeted the mTOR signaling complex in an attempt to develop biologically based therapies for inoperable, NF1-associated progressive PN (NF1-PPN). We specifically selected sirolimus, an allosteric inhibitor of mTOR complex 1, because it is currently FDA approved as an anti-rejection medication for solid organ and bone marrow transplant,[21] and dosing in young children is well established and safe over long periods.

We previously described the results of stratum 2 of a 2-strata phase II clinical trial of sirolimus for the treatment of inoperable, NF1-associated nonprogressive PN.[22] Herein we report the results of stratum 1, which enrolled subjects with inoperable NF1-PPN. We sought to determine whether sirolimus safely and tolerably increases time to progression (TTP) in subjects with NF1-PPN. Volumetric MRI analysis conducted at regular intervals was used to determine TTP relative to baseline imaging. We also evaluated the effects of treatment with sirolimus on pain and QoL using patient-reported outcome (PRO) measures.

Methods

Study Design and Population

Subjects were enrolled at 1 of 9 Department of Defense–funded NF Clinical Trials Consortium (NFCTC) sites. Inclusion criteria were age ≥3 years with a diagnosis of NF1 and an unresectable PN with the potential to cause significant morbidity as previously described.[22] Subjects with paraspinal PNs were eligible for this trial. PNs had to be amenable to volumetric MRI analysis. Subjects may have previously received tumor-directed therapy but must have recovered from the acute toxic effects of all therapy. Stratum 1 enrolled only subjects with PPN (defined as a new PN or an increase in PN size demonstrated on MRI scans done within 1 y based on volumetric [≥20% in volume], area [≥13% in the product of the 2 longest perpendicular diameters], or linear [≥6% in longest diameter] measurements). Informed consent was obtained from the patient, parent, or guardian according to institutional review board guidelines. Other inclusion and exclusion criteria were outlined in the previous report.[22]

Therapy

Subjects initially were allowed to remain on study for up to 5 years (60 cycles), as long as they did not experience progression (as defined below) or significant toxicity from sirolimus, though the study was later amended to allow subjects to remain on study only up to 2 years (26 cycles). The starting dose of sirolimus (1 mL = 1 mg) was 0.8 mg/m^2 body surface area by mouth twice daily for a 28-day course. As outlined in the report of subjects on stratum 2,[22] dosing was pharmacokinetically guided to achieve a trough blood concentration of 10–15 ng/mL, based on an effective sirolimus target reported in patients with tuberous sclerosis complex–associated subependymal giant cell astrocytoma.[23] Sirolimus concentration measurements were performed at steady state following 7–10 days of treatment, then every 2 weeks until stable (defined as 2 consecutive trough concentrations in target range), and finally once per course. Sirolimus whole blood concentrations were centrally determined by a validated tandem mass spectrometry assay, as previously described.[24] Bayesian estimation methods were used to determine pharmacokinetically guided dosing, as previously described.[22]

Evaluations

Subjects underwent anatomic imaging via noncontrast axial and coronal short T1 inversion recovery MRI obtained at enrollment, after every 3 courses until course 9, then after every 6 courses, and at end of therapy. Tumor size was assessed with volumetric analysis performed centrally at the National Cancer Institute (NCI), as previously reported.[6,22,25] Toxicity was monitored with physical examination and laboratory studies (including blood count, fasting glucose and lipid panel, and a comprehensive metabolic panel) monthly for the first 3 courses, and then every 3 courses. Optional health-related QoL and pain intensity assessments were completed by study subjects and/or parent proxy at the same interval of MRI testing. The PRO measures included the PedsQL 4.0 Generic Core Scales (for subjects ages 5–25 y and parents of subjects ages 2–18 y; higher scores [0–100] = better QoL) and the Functional Assessment of Cancer Therapy–General (FACT-G) (for ages ≥25 y) to assess general health-related QoL. Subjects ages ≥5 years completed a visual analog scale (VAS) of 0–100, with higher scores indicating greater pain, to rate the intensity of their worst pain during the past week, which included either the PedsQL Pediatric Pain Questionnaire (for subjects 5–18 y and their parents) or the Short-Form McGill Pain Questionnaire (≥18 y). These measures are described in detail in our report of stratum 2.[22]

Response and Toxicity

For response evaluation, volumetric measurements on follow-up scans were compared with the pretreatment PN volume. Complete response was defined as complete resolution of all measurable PNs. Partial response was defined as a ≥20% reduction in the sum of the volume of all index PN lesions. Stable disease was defined as <20% increase and <20% decrease in the sum of the volumes of all index PN lesions. Progressive disease was defined as ≥20% increase in the volume of at least one of the index PNs compared with the pretreatment volume measured. The appearance of new discrete subcutaneous neurofibromas did not qualify for disease progression, nor did the occurrence of new or increased symptoms without MRI evidence for progression. Subjects who completed at least 3 courses of therapy with follow-up MRI scans were evaluable for response. PN growth rates on treatment (percent change in volume/y) were calculated as previously described.[6] In addition, for a subset of patients who had MRI scans suitable for volumetric analysis prior to enrollment on the study, the pretreatment and on-study growth rates were calculated separately for comparison.

Toxicity was monitored using Common Terminology Criteria for Adverse Events version 3. Subjects were considered evaluable for

toxicity if they received at least one dose of sirolimus and had a "severe" sirolimus-associated toxicity or, in the absence of a "severe" toxicity, completed one full course of therapy. Severe sirolimus toxicity was defined as any of the following toxicities identified during the first 2 courses: grade ≥3 opportunistic infection/*Pneumocystis carinii* pneumonia, grade ≥2 pneumonitis, grade 4 rash, grade ≥3 hypertension, grade ≥3 allergic reaction, worsening renal function, or the development of lymphoma or other cancers. Drug trough target ranges were decreased for the following toxicities if at least possibly due to sirolimus: grade ≥3 neutropenia, anemia, or thrombocytopenia; grade ≥1 hematologic toxicity deemed unsafe to the patient; grade ≥2 pneumonitis; grade ≥1 reduction in glomerular filtration rate; fasting low-density lipoprotein >160 mg/dL; grade ≥2 allergic reaction to sirolimus; grade ≥2 hypertension; grade ≥1 nonhematologic toxicity that was intolerable to the subject or persisted for ≥7 days beyond the start of the next course and was medically significant enough to require treatment interruption. In addition, any grade ≥3 nonhematologic toxicity (except grade 3 nausea/vomiting of <3 d duration), transient grade 3 transaminase elevation, grade 3 gamma-glutamyl transferase elevation, or grade ≥3 hypertriglyceridemia required a target range reduction. Targets were adjusted from 10–15 ng/mL to 7–10 ng/mL, and then to 5–7 ng/mL if needed. Subjects were removed from protocol therapy if they required more than 2 target reductions or experienced a sirolimus-associated toxicity requiring target reduction that did not resolve within 4 weeks of stopping sirolimus.

Statistical Analysis

This study was a single-stage, single-arm phase II trial with TTP as the primary endpoint. The primary trial objective was to determine whether the use of sirolimus in children and adults with NF1-PPN increases TTP. This stratum was designed to test the null hypothesis that the median time to progression is 10.6 months against the alternative that it exceeds 10.6 months at the one-sided 0.05 significance level. The null hypothesis was based on the reported results in the placebo arm of a completed randomized, double-blinded, placebo-controlled trial (NCI trial 01-C-0222) that evaluated tipifarnib (R115777) in children with NF1.[26] Using a one-sample nonparametric survival model, 46 patients were required in stratum 1 to achieve 79% power,[27] as implemented in the Southwest Oncology Group Statistical Office, www.swogstat.org/statoolsout.html. NCI trial 01-C-0222 enrolled 60 eligible patients; 29 were randomized to placebo. As a secondary analysis, we compared our sirolimus group with the placebo group from the NCI trial using the log-rank test. With these sample sizes, this test at the one-sided 0.10 significance level would have 77% power to detect an increase of the median time to progression from 10.6 months on placebo to 18 months on sirolimus based on an exponential model (SAS v9.1.3 Proc Power). In order to allow for a valid comparison of TTP on this trial compared with the placebo arm of the tipifarnib trial and to minimize differences in patient characteristics and related factors, the primary trial endpoints and the assessments of the primary endpoint were identical, and the eligibility criteria were nearly identical for both trials.

The general QoL and VAS pain data were summarized with descriptive statistics (means, ranges). Paired *t*-tests were used to assess change, from baseline to course 3 and from baseline to course 6, in the mean scores of the child self-report and parent proxy PedsQL Scales and the overall self-report and parent proxy ratings of pain intensity on the VASs.

Results

Subject Characteristics

Subject age, gender, and racial distribution and the size and location of target PNs were comparable between the sirolimus-treated and the NCI trial placebo group (Table 1). Of the 49 subjects enrolled on stratum 1, one subject had a PN that was not amenable to volumetric analysis and one subject withdrew consent during course 2. A third subject withdrew from the study after developing grade 2 pneumonitis during course 2. Therefore, a total of 46 subjects were evaluable for response, while 48 were evaluable for toxicity. Of the 48 subjects evaluable for toxicity, 2 (4%) were removed from study for toxicity, 3 (6%) for noncompliance, 21 (44%) for tumor progression, 12 (25%) per patient/guardian request, 8 (7%) per physician request, and 2 (4%) because they completed 26 courses of therapy. Due to the change in the allowed time on therapy, a total of 6 subjects had

Table 1. Subject demographics

Participant's' Characteristics	Stratum 1		
	Sirolimus	Placebo[a]	*P*[b]
Subjects enrolled, *n*	29	49	–
Sex, M:F	14:15	25:24	.81
Age, y, median (range)	8.2 (3–17.7)	7.9 (3–45.4)	.69
Race			
White	23 (79.3%)	35 (71.4%)	
Black, African American	4 (13.8%)	6 (12.3%)	
Native Hawaiian or Pacific Islander	1 (3.4%)	0 (0.0%)	
Asian	0 (0.0%)	3 (6.1%)	
Unknown	1 (3.4%)	5 (10.2%)	
Ethnicity			
Hispanic or Latin	1 (3.4%)	6 (12.3%)	
Non-Hispanic	28 (96.6%)	40 (81.6%)	
Unknown	0 (0.0%)	3 (6.1%)	
Target PNs, *n*	31	53	–
Target PN volume, mL, median (range)	316 (39.6–4896)	186 (13–4808)	.23
Target PN location			.59
Trunk	11	17	
Head/neck	4	12	
Neck/chest	9	8	
Head	3	5	
Trunk/extremity	3	7	
Extremity	1	4	

[a]Stratum 1 from the STOPN trial compared with placebo group from NCI trial 01-C-0222.
[b]*P*-values for sex and location are based on χ^2 test. *P*-values for age and volume are based on Wilcoxon rank-sum test. All *P*-values are 2-sided.

2 years or more of therapy; the longest time on therapy was 36 cycles.

Forty-three subjects completed PRO assessments evaluating QoL and pain. Of these, 5 were adults who did not complete either the baseline or follow-up evaluation, thus there was no evaluable FACT-G QoL data. Of the remaining 38 participants, 33 parents (mean age of their children = 8.0 y, range 3–16) and 24 children (mean age = 9.6 y, range 5–16) completed the PedsQL QoL scale at baseline and again at course 3 and/or course 6 (5 parents and their children had missing data; 8 children were too young to complete the self-report form, and 1 child was not administered a baseline assessment). Twenty-six subjects (25 children and 1 adult; mean age = 9.9 y, range 5–20) and 24 parents (mean age of their children = 9.5 y, range 5–16) completed the pain VAS at baseline and again at course 3 and/or course 6 (8 children were too young, and the others had missing data). Analyses of later time points were not possible due to transition off study and/or missing data points.

Outcomes

Seventy percent of subjects achieved target drug concentration by course 3 (mean 3.1 courses; range 1–15), and only 2 subjects had not achieved target concentration by course 5. The estimated median TTP of subjects receiving sirolimus was 15.4 months (95% CI: 14.3–23.7 mo) (Fig. 1A), which was significantly longer than 11.9 months ($P < .001$), the median TTP of the placebo arm of NCI 01-C-0222 when calculated using the same software employed to calculate the median TTP in our study (Proc LIFETEST of SAS 9.3). (Of note, the median of 10.6 mo previously reported for the placebo group was computed using different software.) The Kaplan–Meier estimate of the proportion of studies free from progression at 2 years was 0.29 (SE = 0.094). TTP was not influenced by sirolimus trough blood concentration. Subjects with trough blood concentrations >10 ng/mL at least 50% of the time did not have a more prolonged TTP ($P = .52$, two-sided log-rank test). Although there were some differences in the age of the participants between this trial and the placebo arm of the NCI 01-C-0222 trial, there was no statistically significant difference between the median ages of the groups ($P = .69$). Similarly, there was no statistically significant difference ($P = .23$) in the target volumes of these 2 groups. The outcome was analyzed for age at enrollment with a hazard ratio of 0.684 for the sirolimus group ($P = .21$). When analyzed for tumor size at enrollment, the hazard ratio was 0.71 for the sirolimus group ($P = .25$).

No subjects had a partial response. The maximum decrease in PN volume was 17% (Fig. 1B). The median PN growth rate on study was 14.4% per year (range: −7% to 137%). Among the fastest growing PNs, 3 were projected to double in size within a year; 2 of these lesions were diffuse, infiltrative lower-extremity tumors, and another was a paraspinal encapsulated nodular-appearing lesion.[26,28] A total of 7 nodular-appearing lesions were observed; of those, only 2 exhibited rapid progression, while the other 5 had <20% volume increase per year. While tumors continued to grow on sirolimus, no subject has developed a neoplasm (eg, an MPNST) to date.

PN growth rates, both pretreatment and on-study, could be calculated for 23 subjects. In 7 subjects (30%), the growth rate decreased by half while on-study, whereas the growth appeared to accelerate in 2 subjects, and little to no change was observed in the other subjects. Two examples of growth trajectories are shown in Fig. 2.

General quality of life

On the child self-report PedsQL Scale, there was no significant change in the mean total scores from baseline to course 3 ($n = 23$; 65.4–68.2; mean change = 2.8; $t = 1.37$; $P = .1841$) or from baseline to course 6 ($n = 18$; 67.4–69.2; mean change = 1.8; $t = 0.73$; $P = .4736$). No significant change was found from baseline to course 3 or course 6 for any of the domain scores (all P-values >.05), although there was an upward trend in the emotional domain scores from baseline to course 3 ($n = 23$; 65.4–72.6; mean change = 7.2; $t = 2.02$, $P = .0559$).

On the parent proxy report PedsQL Scale, there was no significant change in the mean total scores from baseline to course 3 ($n = 32$; 64.0–64.2; mean change = 0.2; $t = 0.09$; $P = .9281$) or from baseline to course 6 ($n = 25$; 66.8–67.2; mean change = 0.4; $t = 0.12$, $P = .9042$). No significant change was found from

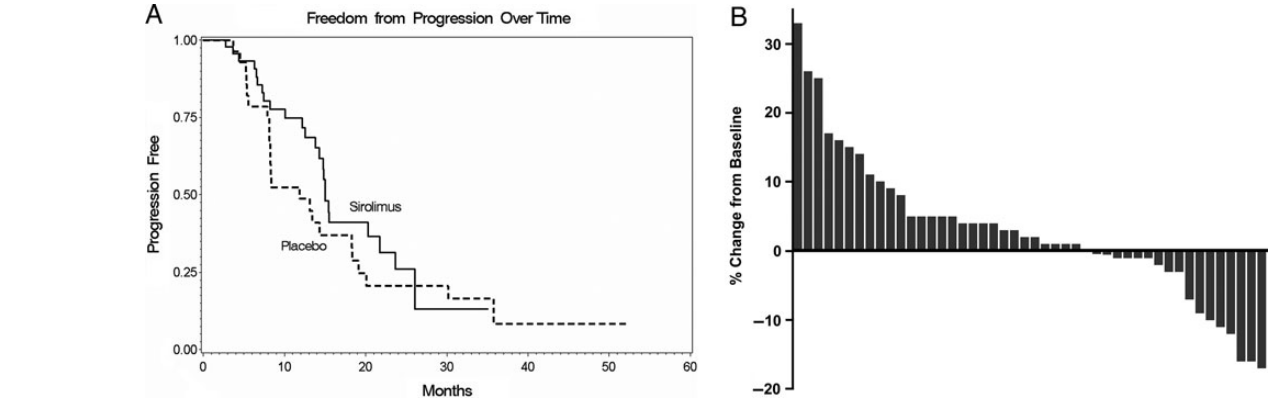

Fig. 1. (A) Progression-free survival on treatment with sirolimus compared with the historical placebo control group of the tipifarnib trial. The median TTP for sirolimus ($n = 46$) was 15.4 months, and for placebo ($n = 29$) 11.9 months (2-tailed $P = <.001$). (B) Waterfall plot showing best response (largest decrease or smallest increase in PN volume, compared with baseline) over the study duration. No subjects achieved a partial response, and the largest volume decrease was 17%.

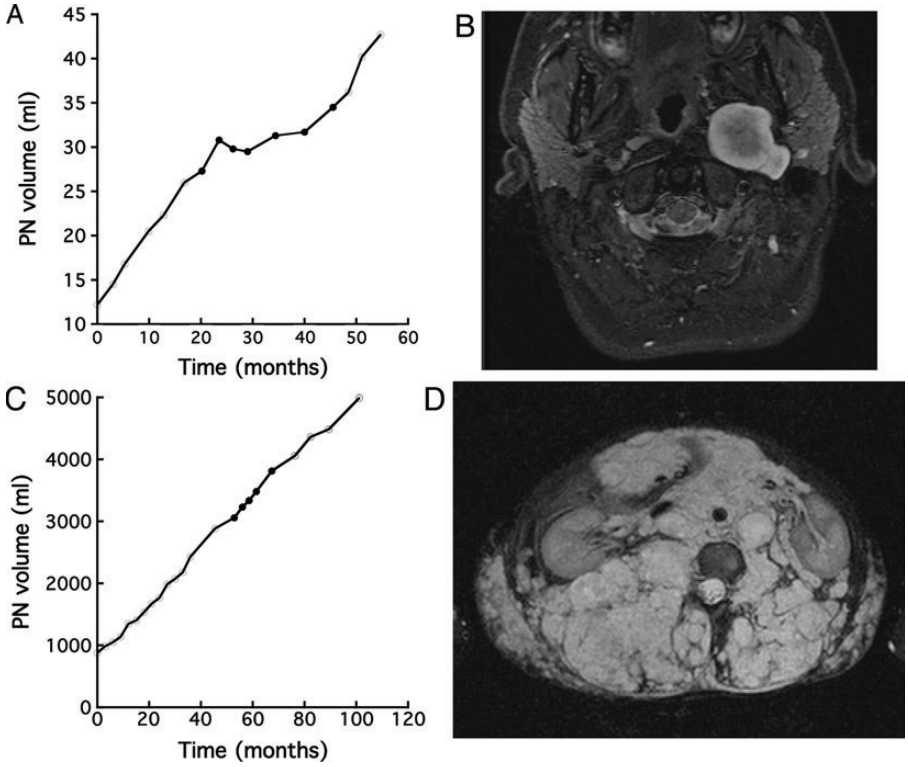

Fig. 2. Examples of longitudinal volumetric measurements from 2 study subjects: (A and B) with nodular lesion, and (C and D) with typical plexiform neurofibroma. Closed symbols correspond to sirolimus treatment; open symbols represent data points before and after treatment with sirolimus.

Table 2. Target level reductions

Subject	Reduction Number	Toxicity	Grade	Course	Resolved	Off Protocol for Toxicity
A	1	Mucositis	2	2	Yes	No
B	1	Neutropenia	3	4	Yes	No
	2	Mucositis/neutropenia	3/3	7	Yes	No
C	1	Hyperlipidemia	*	8	No	No
	2	Hyperlipidemia	*	13	Yes	No
D	1	Hyperlipidemia	*	7	No	No
	2	Hypertension	2	8	No	No
E	1	Neutropenia	3	12	Yes	No

*No grade provided because target adjustments were made below grade 1 levels of low-density lipoprotein.

baseline to course 3 or course 6 for any of the parent reported domain scores (all *P*-values >.05).

Pain intensity

Of the 32 subjects with available pain data at baseline, 75% rated their worst pain over the prior week on the VAS as either being mild ($n = 7$; ratings 5–44 mm), moderate ($n = 5$; ratings 45–74 mm), or severe ($n = 12$; ratings >75 mm), while the ratings of 25% ($n = 8$; ratings <5 mm) indicated no pain based on an established classification system.[29] After treatment with sirolimus, there was no significant change in the subject's mean self-report of pain from baseline to course 3 ($n = 21$; 52.4–57.6; mean change = 5.2; $t = 0.46$, $P = 0.6516$) or baseline to course 6 ($n = 21$; 50.5–56.5; mean change = 6.1; $t = 0.63$; $P = .5339$). The parents' mean ratings of their children' pain also did not change significantly from baseline to course 3 ($n = 23$; 42.7–40.4; mean change = -2.3; $t = -0.24$, $P = .8132$) or baseline to course 6 ($n = 19$; 37.7–39.5; mean change = 1.9; $t = 0.20$, $P = .8428$).

Toxicity

Of the 48 subjects evaluable for toxicity, 2 were removed from the trial for severe sirolimus toxicity (grade 2 pneumonitis), which was reversible in both cases. In addition, 5 subjects required a total of 8 target reductions due to toxicity (Table 2), although

Table 3. Highest toxicity experienced at least possibly related to sirolimus

Highest-Grade Toxicity	Number of Subjects	Percent
1	13	27.1
2	23	47.9
3	11	22.9
4	1	2.1

none required removal from therapy. Thirteen subjects (27%) experienced at most grade 1 toxicity due to sirolimus. The maximum toxicity grade was grade 2 in 23 subjects (48%), grade 3 in 11 subjects (23%), and grade 4 in 1 subject (2%) (Table 3). Thirteen subjects developed mucositis (27%) and 12 (25%) cytopenia (anemia, leukopenia, neutropenia, or lymphopenia) at least possibly related to sirolimus. Nausea or vomiting was seen in 5 subjects (10%), while 4 subjects (8%) developed lipid elevations (in either triglycerides or cholesterol).

Discussion

The primary endpoint of this study was to assess whether the mTOR inhibitor sirolimus would delay TTP in patients with NF1-PPN compared with a historical placebo control group (NCI trial 01-C-0222). The main eligibility criteria for the 2 studies were similar. Sirolimus was well tolerated in NF1 subjects at doses similar to those administered to patients in the transplant setting, and only 5 subjects (10%) had target reductions due to toxicity. Most subjects achieved target sirolimus concentrations by course 3, and all but 2 subjects achieved target concentration by course 5. The TTP of the sirolimus-treated stratum was significantly longer than the historic placebo-treated subjects (15.4 mo compared with 11.9 mo). Based on the comparison of PN growth rates pretreatment and on-study in 23 subjects, the increase in TTP appears to be limited to a subset of subjects rather than representing a modest overall increase. In 7 of 23 (30%) subjects, the PN growth rate decreased sufficiently to predict a doubling in the TTP. This exceeds the reported doubling in TTP in 3 out of 40 (7.5%) patients on the historical placebo control group.

The NCI tipifarnib/placebo trial identified that nodular-appearing lesions had faster growth rates (>30% per y) compared with typical PN. In the present study, only 2 of 7 nodular lesions had similar rapid growth rates, and 5 lesions had <20% change per year. It is thus possible that sirolimus decreased the growth rate of nodular lesions (Fig. 2A). However, additional studies would be required to substantiate these provocative early findings.

While sirolimus prolonged the TTP of NF1-PPN by almost 4 months, in contrast to the efficacy of the mTOR inhibitors for subependymal giant cell astrocytomas in tuberous sclerosis complex (another Ras-pathway disease),[23] sirolimus did not significantly shrink PNs either in the progressive stratum reported herein or in the nonprogressive stratum.[22] To date, the most promising nonsurgical treatment for PNs reported has been imatinib.[30] In that study, PN shrinkage (defined as ≥20% decrease in PN volume) was noted in 17% of subjects; however, all responses occurred in small tumors (<20 mL), unlike the bulky PNs included in our study. A preliminary report from the ongoing phase 2 study of pegylated interferon-alpha 2b also demonstrates prolongation in TTP compared with the historical placebo control group of the NCI trial and minor tumor shrinkage in a few patients.[31]

On PRO measures, the majority of subjects at baseline rated having some degree of pain during the previous week, and no significant group changes were found in overall pain ratings during the first 6 months of treatment. A case study reported pain relief in 3 pediatric patients treated with sirolimus[32]; although some individual subjects in the current trial had increases or decreases in their pain ratings, there was no consistent effect on pain. There also was no significant change in total QoL scores as reported by children or their parents from baseline to 3 or 6 months, indicating neither consistent improvement nor detrimental effect of sirolimus on everyday functioning. However, the children's self-report responses indicated a nonsignificant upward trend in the mean scores of the emotional domain from baseline to 3 months on sirolimus. The reason for this increase is not clear and could be related to the positive feelings that might result from participating in a treatment trial. However, a significant increase in the emotional domain was found in a small sample of children with nonprogressive PNs treated with sirolimus[22] as well as in another study evaluating tipifarnib, a farnesyltransferase inhibitor, in children with NF1-PPN.[26] In contrast, the placebo arm of the tipifarnib trial did not reveal a significant change in emotional domain. It is possible that sirolimus and other drugs acting on the Ras pathway may contribute to these observed changes, since these agents are involved in hippocampal neurogenesis and the regulation of emotions[33] and have been found to decrease depressive-like behavior in both animal[34] and human studies.[35] This hypothesis and the effects of sirolimus on pain will require further investigation.

It is also important to interpret the pain and QoL results in this study with caution, since the PRO assessment was optional and there were missing data. Future clinical trials of agents targeting PNs should make PROs a required evaluation and provide sufficient resources and electronic methods for data collection and management.[36] The inclusion of PROs may provide a valid endpoint for evaluating other important clinical effects of treatment beyond tumor response.[37]

In conclusion, this NFCTC study demonstrated that sirolimus prolongs NF1-PPN TTP by almost 4 months. Although the improvement in TTP is modest, given the lack of significant or frequent toxicity and few other treatment options, the use of sirolimus to slow the growth of PPN should be considered in select patients. Given the need for years of sirolimus administration to achieve this 4-month improvement in TTP, future studies will be required to identify subsets of PN that may be more likely to respond to sirolimus therapy. In addition, sirolimus may be effective when combined with other targeted agents, such as inhibitors of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated protein kinase (ERK), and MAPK/ERK kinase (MEK) pathways. Recent work in both sporadic and NF1-associated MPNST implies that blockade of both mTOR and MEK pathways has synergistic effects and prevents the development of resistance and reactivation of target pathways.[38] A similar strategy may be warranted for PN.

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