Imatinib mesylate for plexiform neurofibromas in patients with neurofibromatosis type 1: a phase 2 trial

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Summary

Background Plexiform neurofibromas are slow-growing chemoradiotherapy-resistant tumours arising in patients with neurofibromatosis type 1 (NF1). Currently, there are no viable therapeutic options for patients with plexiform neurofibromas that cannot be surgically removed because of their proximity to vital body structures. We undertook an open-label phase 2 trial to test whether treatment with imatinib mesylate can decrease the volume burden of clinically significant plexiform neurofibromas in patients with NF1.

Methods Eligible patients had to be aged 3–65 years, and to have NF1 and a clinically significant plexiform neurofibroma. Patients were treated with daily oral imatinib mesylate at 220 mg/m² twice a day for children and 400 mg twice a day for adults for 6 months. The primary endpoint was a 20% or more reduction in plexiform size by sequential volumetric MRI imaging. Clinical data were analysed on an intention-to-treat basis; a secondary analysis was also done for those patients able to take imatinib mesylate for 6 months. This trial is registered with ClinicalTrials.gov, number NCT01673009.

Findings Six of 36 patients (17%, 95% CI 6–33), enrolled on an intention-to-treat basis, had an objective response to imatinib mesylate, with a 20% or more decrease in tumour volume. Of the 23 patients who received imatinib mesylate for at least 6 months, six (26%, 95% CI 10–48) had a 20% or more decrease in volume of one or more plexiform tumours. The most common adverse events were skin rash (five patients) and oedema with weight gain (six). More serious adverse events included reversible grade 3 neutropenia (two), grade 4 hyperglycaemia (one), and grade 4 increases in aminotransferase concentrations (one).

Interpretation Imatinib mesylate could be used to treat plexiform neurofibromas in patients with NF1. A multi-institutional clinical trial is warranted to confirm these results.

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Introduction

Neurofibromatosis type 1 (NF1) is the most common human genetic cancer predisposition syndrome, causing substantial morbidity and mortality in roughly one in 3000 individuals.[1,2] The disorder results from autosomal dominant mutations in the NF1 tumour suppressor gene that encodes a Ras GTPase named neurofibromin.[3] Deficiency of neurofibromin leads to hyperactivation of the Ras signalling cascade and other signal transduction networks.[4,5] In around 40% of patients with NF1,[6] the aberrations in these cellular signalling networks culminate in development of tumours known as plexiform neurofibromas, which occur as multiple primary tumours, each with their own growth characteristics. They arise from loss of heterozygosity in individual Schwann cells in almost any anatomical location where Schwann cells reside. These locally invasive tumours can be painful, disfiguring, and life-threatening when localised near vital structures such as upper airway or major nerves and blood vessels.[7,8] Due to their slow-growing nature, plexiform neurofibromas are highly refractory to radiotherapy and chemotherapy, and surgery is often extremely challenging because of localisation of these tumours.[7] In view of the limited viable treatment options, there is an urgent medical need for novel therapeutic approaches to allow successful management of plexiform neurofibromas.

The kinase inhibitor imatinib mesylate reduces tumour size of plexiform neurofibromas in a preclinical mouse model of NF1 that fully recapitulates the development of plexiform neurofibromas detected in patients with NF1.[9,10] Mechanistically, this effect is attributed at least in part to targeting cellular phospho-signalling cascades in the tumour microenvironment.[8,11] On the basis of these findings, we administered imatinib mesylate (350 mg/m² per day) to a patient with NF1 with life-threatening airway compression by a plexiform neurofibroma, and achieved a greater than 50% reduction in tumour size within 3 months of therapy, resulting in substantial symptomatic relief.[8] To build on these findings and establish whether imatinib mesylate could decrease the volume of individual plexiform neurofibromas in other patients with NF1, we undertook a phase 2 open-label trial of this oral small-molecule kinase inhibitor in patients with NF1 and clinically significant plexiform neurofibromas.

Methods

Patients

Patients were recruited from the Indiana University School of Medicine Neurofibromatosis Clinic, Indianapolis, IN, USA, and the Neurofibromatosis Clinic at the University of Texas Southwestern Medical Center/Children's Medical Center, Dallas, TX, USA, or by self-referral. Patient entry criteria included: age of 3–65 years; clinical diagnosis of NF1; and presence of clinically significant plexiform neurofibromas defined as potentially life-threatening tumours, tumours impinging on vital structures, or tumours that significantly impair patients' quality of life from a subjective standpoint because of pain or other symptoms (eg, dyspnoea, urinary dysfunction, and weakness, dependent on location of individual plexiform tumours). Furthermore, patients must have had at least one plexiform neurofibroma that could be measured by MRI (at least 10 mm in largest dimensions) to allow objective measurements of tumour response to treatment. Eligible patients needed to have had a life expectancy of more than 2 months, Karnofsky[12] or Lansky[13] performance score of 80% or more, and adequate end-organ function (defined as total bilirubin concentration <1·5×upper limit of normal [ULN], aspartate aminotransferase and alanine aminotransferase <2·5×ULN, creatinine <1·5×ULN, absolute neutrophil count >1·5×10⁹/L, and platelets >100×10⁹/L). Women of childbearing potential had to have had a negative pregnancy test within 7 days before study enrolment, and men and women had to agree to use a barrier birth-control method during the study and for 3 months after discontinuation of study drug.

Key exclusion criteria were: exposure to chemotherapy or any other investigational agents within 28 days before enrolment on study; history of another malignancy within 5 years; known brain metastases; New York Heart Association Criteria for class III or IV heart failure;[14] other uncontrolled medical disease; pregnancy or breast-feeding; HIV infection; history of radiation to 25% or more of bone marrow space; history of a major surgery within 2 weeks before study entry; and significant concern for medical non-compliance.

The protocol was approved by the institutional review boards at Indiana University School of Medicine and the University of Texas Southwestern-Medical School, Dallas, and written informed consent was obtained from all patients.

Procedures

On confirmation of eligibility and study recruitment, patients were imaged with MRI short tau inversion recovery (STIR) imaging to measure baseline tumour size (figure 1). Plasma specimens for future baseline tumour biomarker measurements were obtained in addition to routine laboratory tests. Imatinib mesylate (Novartis, East Hanover, NJ, USA) was administered orally at the dose of 220 mg/m² twice a day for children and 400 mg twice a day for adults (dosing at the maximum tolerated dose per recommendations by study drug manufacturer). Patients returned to clinic for follow-up visits including review of symptoms, physical examination, complete blood count, and serum chemistries weekly for 2 weeks, then every other week for 2 weeks, then monthly for 1 month, then every 3 months thereafter (figure 1), or as clinically indicated. Follow-up MRI tumour measurements were done after 2 months of treatment, then at 6 months, 1 year, and yearly thereafter. Plasma samples for follow-up correlative tumour marker studies were obtained at study enrolment and 6 months after beginning the study drug and stored for future analysis. Treatment with imatinib mesylate was continued for 6 months with an option to continue as long as the patient showed benefit from the study drug and there were no safety concerns. Major criteria for discontinuation of study drug included: evidence of clinically and radiologically progressive disease; patient's or parent's request; and adverse effects requiring removal from study. Daily diaries were kept by patients or parents to monitor compliance and toxicities. In view of the variation of symptoms in patients and absence of a validated quality-of-life instrument for neurofibromatosis, no quantitative assessment was done beyond the patient's subjective impression.

Total body MRI with STIR, which suppresses fat signal and accentuates the water signal, was used for imaging at recruitment and throughout the trial. Neurofibromas typically show hyperintense signal on T2 weighted imaging. With fat suppression, STIR is able to easily differentiate neurofibromas from surrounding tissue without the addition of intravenous gadolinium. All imaging was done on a 1·5 T clinical MRI (Magnetom Avanto, Siemens Medical Solutions, Malvern, PA, USA) in the coronal and axial planes at 4 mm gapless slice thickness. Criteria for selection of plexiforms to measure included: tumours likely contributing to clinical problems; images distinct enough for accurate measure; and tumours large enough (≥10 mm) with a minimum of three MRI slices for

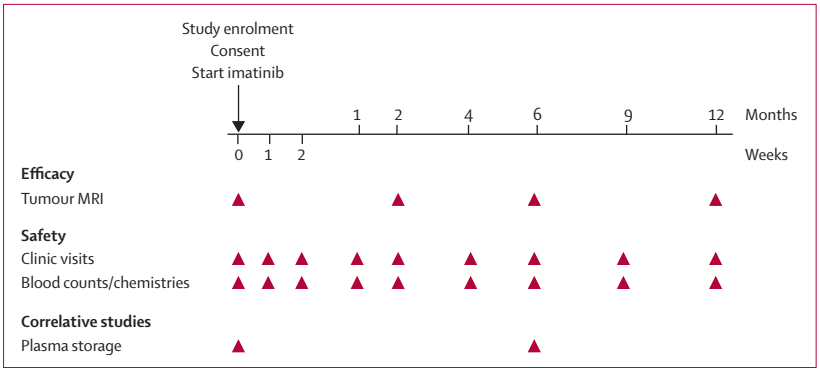

Figure 1: **Study design**
Red triangles indicate timing of designated assessments.

	Enrolled patients (n=36)				Evaluable patients (n=23)			
	Total	Paediatric group (n=13)	Adolescent group (n=12)	Adult group (n=11)	Total	Paediatric group (n=9)	Adolescent group (n=8)	Adult group (n=6)
Age (years)								
Range	3–52	3–9	10–17	19–52	3–33	3–9	11–17	19–33
Median (IQR)	13 (7·5–23)	4 (3·5–8)	13 (11–14)	28 (22–37)	11 (8–19)	7 (4–8·5)	13 (11–14·5)	26 (22–32)
Sex								
Male	19	9	6	4	15	6	5	4
Female	17	4	6	7	8	3	3	2
Number plexiforms	107	..	..	..	69	..	..	..
Median per patient (IQR)	3 (2–4)	..	..	..	3 (2–4)	..	..	..
Plexiform site								
Head/neck	15	..	..	..	11	..	..	..
Abdomen/pelvis	5	..	..	..	5	..	..	..
Extremity	1	..	..	..	1	..	..	..
Paraspinal	4	..	..	..	2	..	..	..
Generalised	11	..	..	..	4	..	..	..

Table 1: **Patient characteristics**

	Reason to discontinue drug	Duration
4-year-old boy	Patient refused to take drug; parent decision	3 months
3-year-old boy	Initial MRI and follow-up CT not comparable; primary medical doctor decision	2 months
5-year-old boy	MRIs not comparable for volumetric determination; principal investigator decision	6 months
3-year-old girl	Patient refused to take drug; parent decision	1 month
14-year-old girl	Resection of plexiforms; parent decision	2 months
13-year-old girl	Non-compliance; parent decision	5 months
10-year-old girl	Oedema, felt to be drug related; parent decision	2 months
13-year-old boy	Unable to take drug consistently due to extensive gastointestinal plexiforms; doctor/parent decision	12 months*
52-year-old woman	Minor anorexia, weight loss; patient decision	3 months
37-year-old woman	Plexiforms too small for volumetric analysis; study investigator decision	12 months
28-year-old woman	Grade 3–4 drug-related oedema, seizure; doctor decision	4 months
21-year-old woman	Grade 4 hepatic toxicity; doctor decision	5 months
48-year-old woman	Drug related oedema, weight gain, gastrointestinal toxicity; patient decision	4 months

*Could take only an occasional dose and then came off drug for weeks at a time. Parents wished to continue to try dosing, but without success.

Table 2: **Reasons for exclusion from analysis of evaluable patients**

accurate volumetric determination. Volumes of up to five plexiform neurofibromas per patient were measured with a manual volumetric technique.[15,16] Areas of each tumour were measured on sequential MRI sections by manually outlining the tumour, and the sum of area was multiplied by the MRI slice thickness to calculate the tumour volume.[15,16] Individual plexiform neurofibromas were measured with the same technique across sequential scans, matching anatomical features of the tumour and surrounding structures from scan to scan. Consistent with previous clinical trials in neurofibromatosis tumours,[17–19,23] response was defined as a sustained 20% or more reduction in tumour volume from baseline in two or more sequential MRIs, including the MRI at the conclusion of the study protocol. Progression was defined as a 20% or more increase in tumour volume, and tumours that showed less than 20% reduction and less than 20% increase in volume were categorised as stable. Since there has so far been no effective therapy for plexiform neurofibromas, and taking into account the presence of multiple individual tumours, our primary goal was to establish whether any individual plexiform neurofibromas could respond to imatinib mesylate. Inherent in that endpoint is the recognition that with individual tumour growth qualities and molecular evolution, some plexiform neurofibromas might respond, whereas others might remain stable or continue to grow.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria (version 3.0). Imatinib mesylate dose modifications were allowed for grade 3 and 4 adverse effects and for grade 2 skin rash deemed to be due to the study drug. The principal investigator was required to notify the institutional review board, US Food and Drug Administration, and study drug manufacturer about occurrence of serious adverse effects within 3 working days.

Statistical analysis

The primary outcome was the proportion of patients who achieved an objective tumour response with imatinib mesylate evidenced by volumetric tumour measurements

of MRI images, with an objective response defined as a 20% or more decrease in tumour volume. Clinical data were analysed on an intention-to-treat basis by calculating 95% CIs for the response rate. To gain a better sense of the activity of the study drug on plexiform neurofibromas, given that some patients withdrew from study, we did a secondary analysis in the 23 patients who completed 6 months of treatment with imatinib mesylate. To gain a better sense of the activity of the study drug on plexiform neurofibormas, we did a secondary analysis in the 23 patients who completed 6 months of treatment with imatinib mesylate. Again, 95% CIs were calculated for the response rate to imatinib mesylate producing a 20% or more decrease in tumour volume. The prespecified secondary outcomes were to assess safety and tolerability of imatinib mesylate in NF1 patients with plexiform neurofibromas. R, version 2.14.1, was used for statistical analyses.

The study is registered with ClinicalTrials.gov, number NCT01673009.

Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the study report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 1, 2006, and March 30, 2009, 36 patients were enrolled (table 1), three patients from the University of Texas Southwestern and 33 from Indiana University. Of the 36 patients enrolled (19 male and 17 female), the median age was 13 years (IQR 7·5–23; table 1). The study group included patients within the age range of 3–52 years; most patients (n=17) were children and adolescents (table 1). The localisation of plexiform neurofibromas varied, with almost half of the tumours localised in the head and neck region (table 1). 23 (64%) patients completed 6 months of study drug and were evaluable; their median age was 11 years (IQR 8–19). The remaining 13 patients withdrew from the study prematurely (table 2). Specifically, nine patients elected to discontinue the study drug before 6 months because of minor problems with taking study drug or drug side-effects largely a result of dosing at the maximum tolerated dose. Two patients discontinued the study drug because of their local physician's concern for tumour progression that could not be verified objectively because of CT/MRI scan incompatibility. Finally, two patients discontinued the study drug because one underwent tumour resection and the other had plexiforms too small to be measured volumetrically. One of the study patients is still receiving imatinib mesylate.

On an intention-to-treat basis, six of 36 patients (17%; 95% CI 6–33) had an objective response to imatinib mesylate with at least a 20% decrease in tumour volume in one or more plexiform neurofibromas. In the evaluable study population of patients who received imatinib mesylate for at least 6 months, six (26%; 95% CI 10–48) had a 20% or greater decrease in volume of one or more plexiform tumours (figure 2). In these 23 evaluable patients, 69 plexiforms were assessed, with an average of three plexiforms per patient. To adjust for clustering that might occur within individual patients, an analysis was done for correlated binary outcome. The difference was not significant between adult and paediatric patients (odds ratio 1·12, 95% CI 0·19–6·5; p=0·89). When we considered individual tumours in the evaluable patients, eight (12%, 95% CI 5–21) of 69 tumours were reduced in volume by 20–38% (median 26·5%, IQR 25–29·5) after treatment with imatinib mesylate (figure 2). The median time to the first measurable response in evaluable patients

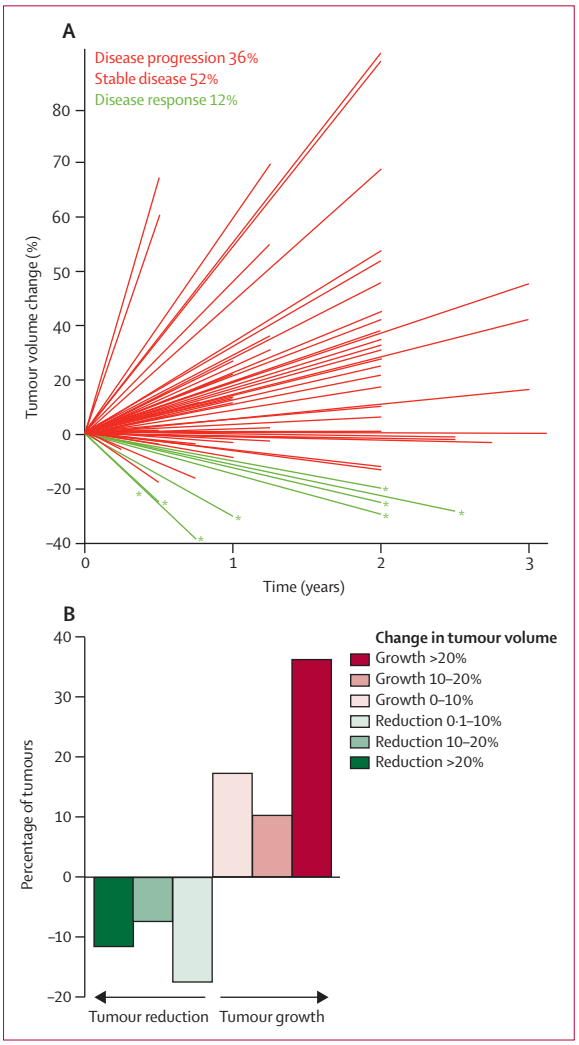

Figure 2: **Change in volume of plexiform neurofibromas in patients with NF1**
(A) Green lines with asterisks represent tumours that decreased in volume over time as evidenced by MRI measurements; red lines represent growing tumours including those not decreasing by ≥20% in volume. (B) Relative percentage of tumours in patients given imatinib mesylate, expressed by percentage change in tumour volume.

	Number of patients	Number (%) responsive*	Number (%) stable†	Number (%) progressive‡
Tumour response according to age				
3–9 years	23	3 (13%)	10 (43%)	10 (43%)
10–18 years	23	2 (9%)	13 (56%)	8 (35%)
≥19 years	23	3 (13%)	13 (56%)	7 (30%)
Total	69	8 (12%)	36 (52%)	25 (36%)
Tumour response according to location				
Head and neck	33	7 (21%)	15 (45%)	11 (33%)
Trunk	29	1 (3%)	17 (59%)	11 (38%)
Extremities	7	0 (0%)	4 (57%)	3 (43%)
Total	69	8 (12%)	36 (52%)	25 (36%)
Tumour response according to tumour size (cm^3)				
1–5	28	4 (14%)	14 (50%)	10 (36%)
5–10	15	3 (20%)	9 (60%)	3 (20%)
10–20	10	1 (10%)	8 (80%)	1 (10%)
>20	16	0 (0%)	5 (31%)	11 (69%)

*Defined as ≥20% decrease in volume. †Defined as <20% decrease or increase in volume. ‡Defined as ≥20% increase in volume.

Table 3: **Plexiform neurofibroma response by age, location, and plexiform size**

	Number of events	Toxicity
Grade 1	8	Oedema (3), nausea (1), depression (1), abdominal cramping (1), joint aches (1), neuropathy (1)
Grade 2	11	Diarrhoea-incontinence (1), hyperbilirubinemia (1), weight gain (1), dyspnoea (1), anorexia (1), rash (1), pain (3), oedema (1), ataxia (1)
Grade 3	10	Rash (4), seizure (1), neutropenia (2), weight gain (1), motor neuropathy (1), pain (1)
Grade 4	2	Elevated aminotransferases (1), hyperglycaemia (1, diabetic patient)

Numbers of patients are shown in parentheses.

Table 4: **Adverse events, by grade**

was 4 months (IQR 2–6) in children and 8 months (IQR 6–12) in adults. However, with the small numbers of patients treated in this trial, this difference was not significant (p=0·83, log-rank test for correlated data).

We noted heterogeneity in response for different tumours within individual patients. 19 evaluable patients had multiple measurable tumours, with 12 (63%) of these patients showing a heterogeneous response (a mix of responsive, stable, or progressive plexiforms), which probably results from the biology of plexiform neurofibromas arising as genetically distinct primary tumours. When the data were analysed with respect to age, tumour location, and size (table 3), we recorded no significant differences. However, we noted that larger tumours tended to be less responsive (perhaps indicating difficulty in drug delivery into large solid tumours), and that head and neck tumours seemed to be more responsive than plexiforms localised in other body parts across age groups.

Seven evaluable study patients (30%) reported subjective improvement in disease symptoms, including improved dyspnoea noted at ear, nose, and throat evaluation and resolution of snoring or disruptive sleep pattern, improved bladder control as evidenced by loss of need for self-catheterisation, and decreased pain and improved sensory or motor symptoms in two patients. Specifically, one patient with cervical-cord involvement had a decrease in pain and tingling of the hands with improved grip strength, and another patient with lumbar cord plexiforms had improved leg strength, which allowed him to walk unassisted.

19 of 36 enrolled patients needed dose reductions or interruptions because of treatment-related side-effects. The most common adverse effects in the total study intention-to-treat population were skin rash and oedema (table 4). Other adverse events included reversible grade 3 neutropenia, weight gain, and grade 4 elevation of aminotransferase concentrations. One patient died during the study. This patient had a known seizure disorder with an upper respiratory infection, during which the study drug was held. The patient had a seizure leading to airway obstruction and aspiration. The death was believed to be unrelated to the study treatment.

Discussion

Findings from this open-label phase 2 trial suggest that high-dose oral imatinib mesylate may have a role in the treatment of clinically significant plexiform neurofibromas in children and adults with NF1 (panel). To our knowledge, this is the first successful reduction in volume of plexiform neurofibromas using targeted oral chemotherapy.

We noted objective responses to imatinib mesylate in 26% of the evaluable patients enrolled in the study. The rationale for presentation of the data in terms of evaluable patients is based on our observations that most patients who came off study did so because of issues related to compliance, and they did not take the drug long enough to test the biological effect. The reasons for poor compliance relate to the biology of the tumour and the initial dosing of drug. Overwhelmingly, plexiform tumours are slow growing, and consequently many patients have been living with them for many years. Thus, unlike patients with highly malignant tumours who are tolerant of at least some side-effects, patients with plexiform neurofibromas have a very low threshold for any drug-related discomfort. The initial choice for dosing of drug also contributed to the poor compliance. Given that there are no known active or effective agents for plexiforms, we decided that initial dosing would be at the previously established maximal tolerated dose to see whether imatinib was active for any plexiforms. Collectively, these factors result in a high likelihood of having minor and major side-effects in a population of patients that would not tolerate

side-effects. This resulted in refusal to take the drug and compliance issues (nine of the 13 patients who came off study). In fact, because taking the study drug was problematic for these patients, we have substantially modified the dosing regimen in the ongoing follow-up trial (NCT01140360). In that study, imatinib is taken orally with a starting dose of 100 mg twice a day for patients with a body surface area (BSA) greater than or equal to 1·8 m² or 55 mg/m² twice daily for patients with a BSA of less than 1·8 m². For patients with a BSA of at least 1·8 m², the dose is increased by increments of 100 mg twice a day every 2 weeks as tolerated up to a maximum dose of 400 mg twice a day. For patients with a BSA of less than 1·8 m² the dose is increased by increments of 55 mg/m² twice a day every 2 weeks as tolerated up to a maximum dose of 220 mg/m² twice a day, with improvement in drug tolerability recorded (unpublished data). Of the other four patients who discontinued treatment, one came off study after what seemed to be an early response, because the parents saw an opportunity to resect the tumour. A second individual was excluded from the study because the tumours were too small to measure volumetrically. Furthermore, two patients withdrew early in the course because of referring physicians' concerns for tumour progression, although these concerns were not confirmed by CT/MRI scans (table 2). At the individual tumour level, 12% shrank by 20–38% in volume. Natural history studies of untreated patients with NF1 report that plexiform tumours never regress, but rather display variable progressive growth[17] documented by continued slow increase in tumour volume over time.[17] By contrast with previous data, we noted a profound response (≥20% decrease in tumour volume) to the study drug in a subset of tumours, some of which reduced in volume by almost 40% with a median reduction of 26·5% (IQR 25–29·5). Furthermore, a large subset of tumours in evaluable patients had a decrease in tumour volume compared with historical controls, but less than the 20% threshold (figure 2). Importantly, tumour response was associated with substantial subjective improvement of symptoms reported by patients, including in some patients in whom tumours were reduced by less than the 20% threshold. In several cases, the observed clinical improvement was remarkable, including better airway patency, regained bladder control, and improved lower extremity motor symptoms. The response of plexiform neurofibromas to imatinib might partly be due to cells expressing the c-kit receptor in the tumour microenvironment as characterised in the pre-clinical model.[8]

The disease response to the study drug varied not only between patients, but also between different tumours in individual patients. Additionally, the median time to the first measurable response in paediatric patients tended to be shorter than in adult patients. This observation could open new insights into the understanding of pathobiology of plexiform neurofibromas, and potentially unravel novel therapeutic targets. We are actively pursuing these hypotheses using a systems-biology approach, since the findings might facilitate customised treatment and screening programmes in patients with this common genetic disorder.

Our study has limitations, which include the small sample size and significant heterogeneity of patient population with respect to age, tumour location, and disease extent. This pilot study takes a necessary step towards development of effective therapeutic strategies for NF1-related plexiform neurofibromas by addressing whether individual tumours can respond to targeted therapy. The inclusion criteria were purposefully kept very broad and inclusive to establish whether imatinib mesylate showed any activity without restriction of entry criteria other than having NF1 and a clinically significant plexiform neurofibroma within the specified age limitations (age 3–65 years). A large-scale, multi-institutional non-placebo phase 3 clinical trial is needed to confirm the results of this pilot study with more open eligibility criteria that avoid the limitations of smaller scale phase 2 trials. A placebo-controlled phase 3 trial would be unethical since this report establishes the activity of imatinib mesylate against a fraction of plexiform neurofibromas and there are no other treatments

***Panel:* Research in context**

Systematic review

We searched PubMed for all publications in 2000–12, including clinical trials, meta-analysis, and reviews, with the terms "neurofibromatosis type 1", and "plexiform". We identified three clinical trials of therapies for neurofibromatosis type 1 (NF1) plexiform tumours including a phase 1 trial of tipifarnib (Johnson & Johnson, Beerse, Belgium)[19] without objective response, and a phase 1 trial of pirfenidone (Solanan, Dallas, USA)[18] without objective response using volumetric measures to detect 20% reduction as the response threshold. Finally, a phase 1 trial of pegylated interferon-alpha-2b[20] in paediatric NF1 patients with plexiform neurofibromas showed tumour reduction in five of 17 patients that were assessed by volumetric measurements of the tumour, but only one individual had a tumour response that was larger than 20%.

Interpretation

Our findings show radiographic volumetric tumour reduction in response to medical therapy in patients with NF1 plexiform neurofibromas with the use of imatinib mesylate. The findings in this study provide the first evidence of an effective therapy for a subgroup of NF1-related plexiform neurofibromas and a validation of the published response of plexiform neurofibromas to imatinib in a genetic mouse model,[8] which puts in place a translational model whereby other drugs can be screened for activity against plexiform neurofibromas in the genetic NF1 mouse model before moving into clinical trials.

available. On the basis of the data in this trial, we believe a minimum of 1 year of assessment on treatment is important to allow patients to show responsiveness. Finally, many study patients reported subjective improvement of quality of life or clinical symptoms that frequently (but not always) correlate with tumour response as evidenced by sequential MRIs. We are developing questionnaires and other study methods to allow quantification of subjective clinical improvement and address potential placebo effects in future clinical trials in this patient population.

Contributors

KAR, FCY, CYH, JMC, TAV, LFP, JWF, DAI, and DWC were involved in the design and development of the study. KAR, CYH, JMC, TAV, LFP, KRP, MWL, and LCM were involved in the writing and review of the protocol. KAR, DCB, CMH, LEW, KRP, JBT, MWL, MRS, and CJD were responsible for patient referral, enrolment, and follow-up. KAR, DCB, CYH, CMH, MKEB, JBT, KWS, MWL, and MRS were responsible for data collection. KAR, GN, FCY, JMC, TAV, and MY did the biostatistical analyses. KAR, GN, CYH, GDH, MKEB, MDC, and JWF did image analyses. KAR, GN, FCY, CYH, JMC, TAV, SCD, CMH, MY, MDC, KWS, DAI, and DWC prepared the manuscript. All authors have seen and approved the final draft.

Conflicts of interest

We declare that we have no conflicts of interest.

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