Characterization of Cardiac Function by Echocardiographic Global Longitudinal Strain in a Cohort of Children with Neurofibromatosis Type 1 Treated with Selumetinib

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Abstract

Background Plexiform neurofibromas are benign neoplasms that develop in 20–50% children with neurofibromatosis type 1 (NF1). Selumetinib was approved as treatment for symptomatic and inoperable plexiform neurofibromas. Subclinical left ventricular ejection fraction reduction is a less common effect of selumetinib.

Objective We aimed to investigate the contractile function of the heart in a cohort of children with NF1 treated with selumetinib.

Methods We designed a cross-sectional study including 17 patients with NF1 who received selumetinib. Echocardiographic parameters were compared with a cohort of 17 healthy children matched by sex and age and another group of 17 children with untreated NF1.

Results Compared with healthy controls, patients with NF1 treated with selumetinib had lower mean values of global longitudinal strain ($-22.9 \pm 2\%$ vs $-25.5 \pm 2\%$; $p = 0.001$), fractional shortening ($36 \pm 4\%$ vs $43 \pm 8\%$; $p = 0.02$) and tricuspid annular plane systolic excursion (19 ± 3 mm vs 23 ± 2 mm; $p = 0.001$); no difference was found in left ventricular ejection fraction ($63 \pm 4\%$ vs $65 \pm 3\%$; $p = 0.2$ respectively). Median treatment time with selumetinib at the time of the echocardiographic evaluation was 22 ± 16 months.

Conclusions Patients with NF1 treated with selumetinib may experience subtle changes in systolic function identified by global longitudinal strain and not revealed by left ventricular ejection fraction. Global longitudinal strain might be useful to monitor cardiac function in this cohort of patients for the duration of therapy.

Thomas Caiffa and Antimo Tessitore contributed equally to this work.

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Key Points

Selumetinib can induce clinical response in paediatric subjects with neurofibromatosis type 1 affected by symptomatic and inoperable plexiform neurofibromas.

The most common clinical side effects of selumetinib include increased creatine phosphokinase and gastrointestinal and dermatological conditions. Another side effect reported in adults and children is an asymptomatic decrease in left ventricular function.

In our cross-sectional study, the contractile function of the heart evaluated with echocardiographic global longitudinal strain was lower in patients with neurofibromatosis type 1 treated with selumetinib compared with healthy age and sex-paired peers, despite values being within the normal range.

Considering the efficacy of selumetinib, it is advisable to continue administration in these patients. Global longitudinal strain could be useful for monitoring cardiac function during a follow-up.

1 Introduction

Neurofibromatosis type 1 (NF1) is a genetically determined disease belonging to a group of conditions known as "RASopathies," in which the RAS-MAPK pathway is mutated [1]. Plexiform neurofibromas (PNs) are benign neoplasms that develop in 20–50% of patients with NF1 [2]. Multiple morbidities may occur, including pain, motor dysfunction and visual loss [3]. Worsening morbidity is associated with the growth of the lesions [4].

The therapeutic medical approach for symptomatic and inoperable PNs is selumetinib, an oral selective mitogen-activated protein kinase kinase inhibitor, recently approved for the treatment of paediatric patients, that can induce tumour regression [2] and clinical improvement [2, 5–10]. Clinical trials to treat PNs with other targeted therapies are ongoing: the mitogen-activated protein kinase kinase inhibitor mirdametinib was tested in a clinical trial for the treatment of PN [11], as well as cabozantinib, a multiple tyrosine kinase inhibitor with targets that include cMET and vascular endothelial growth factor receptor 2 [12] and imatinib or pegylated interferon [13, 14].

Based on pooled data from over 125 treated patients, the most common adverse effects of selumetinib in patients with NF1 are diarrhoea (64%), elevated creatine phosphokinase (63%, mostly asymptomatic), acneiform rash (54%), mucositis (43%) and paronychia (41%) [15]. Another side effect reported in adults and children is an asymptomatic mild decrease of the systolic function [2, 8, 16] measured by left ventricular ejection fraction (LVEF). Global longitudinal strain (GLS) is an echocardiographic analysis based on the speckle tracking technique [17, 18] that provides accurate evaluation of the contractile function of the heart [19] and has been demonstrated useful for early detection of asymptomatic left ventricular dysfunction [20]. Therefore, in this study, we assessed systolic function by left ventricle GLS in a cohort of paediatric patients with NF1 treated with selumetinib compared to a cohort of healthy age- and sex-paired peers.

2 Materials and Methods

This was a cross-sectional study conducted at the Paediatric Cardiology Department of the Institute for Maternal and Child Health IRCCS Burlo Garofolo of Trieste, Trieste, Italy. Patients diagnosed with NF1 according to the latest revised diagnostic criteria [21, 22], followed at our institution and treated with selumetinib were considered eligible for the study. A cohort of healthy children matched by sex and age was also included. In order to avoid biases related to the previously reported difference in GLS between healthy peers and children affected by NF1 [23], a further cohort of children with untreated NF1 was included.

2.1 Echocardiographic Analysis

All echocardiograms were analysed offline with the vendor-independent software TomTec Arena (TomTec-Arena TTA.2, Munich, Germany). Standard echocardiographic windows were used. Cardiac chamber quantification and evaluation of systolic function were performed according to international guidelines [24]. Left ventricular ejection fraction was evaluated using the biplane Simpson method, from apical two- and four-chamber views.

Global longitudinal strain was measured using the TomTec-Arena software on images obtained from three apical views (four-, two- and three-chamber views), using end-diastole and end-systole frames to trace the endocardial borders. These moments were defined by electrocardiogram and aortic valve opening and closure on the left ventricular outflow tract power Doppler. The speckles along the endocardial border throughout the cardiac cycle were tracked automatically by the software. Accurate tracking was assured by visual review of all borders. In case of poor tracking, the border was readjusted manually until adequate tracking was achieved. Normal reference values for GLS were identified according to the meta-analysis published by Levy et al. [25].

2.2 Statistical Analysis

Normally distributed continuous variables were reported with mean ± standard deviation. Cross-sectional comparisons between groups were made by the analysis of variance test on the Gaussian-expressed continuous variables, using the Brown–Forsyte statistic when the assumption of the variables did not occur, or the nonparametric Mann–Whitney test when necessary. The Chi-square test and Fisher's exact test were calculated for discrete variables. A value of $p < 0.05$ was considered statistically significant. The IBM SPSS statistical software (released 2016, IBM SPSS Statistics for Windows, Version 24.0; IBM Corp., Armonk, NY, USA) was used to conduct these analyses.

2.3 Ethics

Ethics committee approval was not requested according to the Italian Law as General Authorization to Process Personal Data for Scientific Research Purposes (Authorization no. 9/2014) declared that retrospective archive studies that use ID codes, preventing the data from being traced back directly to the data subject, do not need ethics approval [26]. According to the Research Institute Policy, parents of admitted children sign an informed consensus for the anonymous use of data. All parents signed an informed consensus for the use of selumetinib in their children.

3 Results

Of the 21 eligible patients with NF1 treated with selumetinib at our institution, four were excluded because of an inadequate echocardiographic window with poor image quality preventing accurate evaluation of GLS. The study population consisted of 17 patients with NF1 treated with selumetinib. A cohort of 17 healthy children matching the former patients in sex and age was included. In addition, a cohort of 17 children with NF1 not receiving selumetinib and not matched by sex and age was included.

Demographic characteristics of the study population and the paired healthy peers are summarised in Table 1. As the pairing was intentional, there are no differences in mean age (13 ± 4 years, $p = 0.93$) and the proportion of male individuals (65%, $p = 1.0$). On echocardiograms, compared with healthy controls, patients with NF1 treated with selumetinib had lower mean values of GLS (−22.9 ± 2% vs −25.5 ± 2%; $p = 0.001$), left ventricular end diastolic diameter (42 ± 4 mm vs 45 ± 5 mm; $p = 0.01$), left ventricular end diastolic volume index (48 ± 9 mL/m^2 vs 57 ± 7 mL/m^2; $p = 0.003$), fractional shortening (36 ± 4% vs 43 ± 8%; $p = 0.02$) and tricuspid annular plane systolic excursion (19 ± 3 mm vs 23 ± 2 mm; $p = 0.001$); no difference in LVEF was found ($p = 0.2$). Figure 1 shows the differences between the two groups in the four most clinically significant variables. Median treatment time with selumetinib at the time of the echocardiographic evaluation was 22 ± 16 months.

In the study population, different time intervals were used to assess whether the length of the treatment was associated with changes in the GLS, but no statistically significant difference was found (see Table 2).

Global longitudinal strain values were similar among patients who experienced other adverse events and who did not (−22.7 ± 2% vs −23.4 ± 2%, respectively; $p = 0.52$) [Table 3].

Characteristics of the study population and patients with untreated NF1 are shown in Table 1 of the Electronic Supplementary Material (ESM). Patients with NF1 treated with selumetinib had lower GLS values (−22.9 ± 2% vs −5.2 ± 2%, $p = 0.001$) and fractional shortening (36 ± 4% vs 39 ± 4%; $p = 0.02$) compared with patients with untreated NF1, while LVEF values were similar (63 ± 4% vs 66 ± 3%; $p = 0.06$). No difference in those echocardiographic parameters was found among patients with untreated NF1 and the healthy control group (Table 2 of the ESM).

4 Discussion

Selumetinib has been used as a medical treatment for children affected by NF1 with inoperable symptomatic PNs since 2016 [2]. Although its efficacy and ability to change the natural history of neurofibromatosis are documented [15], whether long-term administration of selumetinib might be associated with side effects, especially in the paediatric population, has to be investigated. In particular, the major concern is related to possible cardiotoxicity based on the previous literature reporting such a side effect with the use of a mitogen-activated protein kinase inhibitor, potentially due to the direct inhibition of the MAPK pathway [16].

A meta-analysis [16] conducted on an adult population treated with trametinib, selumetinib or cobimetinib reported an increased risk of worsening LVEF and the development of hypertension. Specifically, a study [27] reported in seven patients undergoing treatment with selumetinib plus dacarbazine a decrease in the LVEF, defined as changes of ≥ 10% from baseline with LVEF < 55%. Left ventricular ejection fraction reduction was reported only in one patient belonging to the placebo plus dacarbazine group. Interestingly, in the selumetinib plus dacarbazine group, LVEF eventually returned to values in the normal range spontaneously while

Table 1 Patient characteristics: comparison between patients receiving selumetinib and healthy controls, matched by sex and age

Patient characteristics	Total	Selumetinib	Controls	*p*-value
Age (years)	13 ± 4	13 ± 4	13 ± 4	0.93
Sex (male)	22 (65%)	11 (65%)	11(65%)	1
Weight (kg)	49 ± 16	52 ± 18	47 ± 15	0.39
Percentile of weight (%)	56 ± 29	58 ± 31	54 ± 27	0.68
Height (cm)	153 ± 17	153 ± 16	154 ± 19	0.87
Percentile of height (%)	49 ± 29	47 ± 33	51 ± 26	0.66
BMI (kg/m^2)	20 ± 3	21.3 ± 4	19.1 ± 2.5	0.06
BSA (m^2)	1.4 ± 0.3	1.5 ± 0.33	1.41 ± 0.31	0.52
HR (bpm)	80 ± 13	81 ± 13	79 ± 14	0.62
LA area (cm^2)	11 ± 3	11 ± 2	12 ± 2	0.22
RA area (cm^2)	11 ±2	11 ± 2	11 ± 2	0.78
Aortic root (mm)	25 ± 3	26 ± 4	25 ± 3	0.58
Ascending aorta (mm)	22 ± 3	22 ± 3	22 ± 2	0.44
E/A	1.7 ± 0.4	1.7 ± 0.4	1.7 ± 0.4	0.63
DT (msec)	141 ± 46	143 ± 60	140 ± 29	0.8
E/E'	6.5 ± 1	6.7 ± 1	6.5 ± 1	0.63
TAPSE (mm)	21 ± 3	19 ± 3	23 ± 2	0.001
GLS (%)	−24.2 ± 2	−22.9 ± 2	−25.5 ± 2	0.001
LV mass index (g/m^2)	58.1 ± 9.5	54.3 ± 9.5	61.8 ± 8.2	0.019
LV mass (g)	84.5 ± 25.6	80.9 ± 25.5	88 ± 26	0.42
LVEDD (mm)	43 ± 5	42 ± 4	45 ± 5	0.01
LVEDDi (mm/m^2)	31 ± 5	29 ± 5	33 ± 5	0.07
LVESD (mm)	27 ± 3	27 ± 4	26 ± 2	0.45
LVESDi (mm/m^2)	19 ± 4	19 ± 3	19 ± 4	0.62
IVSd (mm)	7 ± 1	7±1	7 ± 1	0.75
LVPWd (mm)	6 ± 0.8	6 ± 1	6 ± 1	0.68
IVSs (mm)	9.8 ± 1.2	9.6 ± 1.2	10 ± 1	0.25
LVPWs (mm)	10.8 ± 1.4	10.3 ± 1.2	11.4 ± 1.3	0.02
LVEDV (mL)	77 ± 24	73 ± 26	81 ± 22	0.32
LVEDVi (mL/m^2)	53 ± 9	48 ± 9	57 ± 7	0.003
LVESV (mL)	27 ± 10	27 ± 11	27 ± 10	1
LVESVi (mL/m^2)	18 ± 5	18 ± 4	19 ± 5	0.4
LVEF (%)	64 ± 3	63 ± 4	65 ± 3	0.2
Fractional shortening (%)	39 ± 7	36 ± 4	43 ± 8	0.02
Mitral regurgitation (mild)	4 (12%)	2 (12%)	2 (12%)	1
Tricuspidal regurgitation (mild)	17(50%)	9 (53%)	8 (47%)	0.73
Pulmonary regurgitation (mild)	21 (62%)	12 (71%)	9 (53%)	0.29
Aortic regurgitation (mild)	2 (6%)	2 (12%)	0	0.49

*V*alues are given as mean ± standard deviation, *n* (%)

BMI body mass index, *BSA* body surface area, *GLS* global longitudinal strain, *HR* heart rate, *IVSd* interventricular septal end-diastolic thickness, *IVSs* interventricular septal end-systolic thickness, *LA* left atrium, *LVEDD* left ventricular end-diastolic diameter, *LVEDDi* left ventricular end-diastolic diameter index, *LVEDV* left ventricular end-diastolic volume, *LVEDVi* left ventricular end diastolic volume index, *LVEF* left ventricular ejection fraction, *LVESD* left ventricular end-systolic diameter, *LVESDi* left ventricular end-systolic diameter index, *LVESV* left ventricular end-systolic volume, *LVESVi* left ventricular end-systolic volume, *LVPWd* left ventricular posterior wall end-diastolic diameter, *LVPWs* left ventricle posterior wall end-systolic thickness, *RA* right atrium, *TAPSE* tricuspidal annular plane systolic excursion

continuing selumetinib ($n = 4$) and after interruption ($n = 2$) in all six patients with follow-up assessments.

Selumetinib discontinuation due to an asymptomatic decrease in LVEF has also been reported in children affected by NF1. First, it was reported in a pivotal study [2], defined as a dose-limiting adverse effect, in which a > 10% decrease in LVEF (from 65 to 50%) was found in an asymptomatic patient at the first echocardiographic evaluation performed

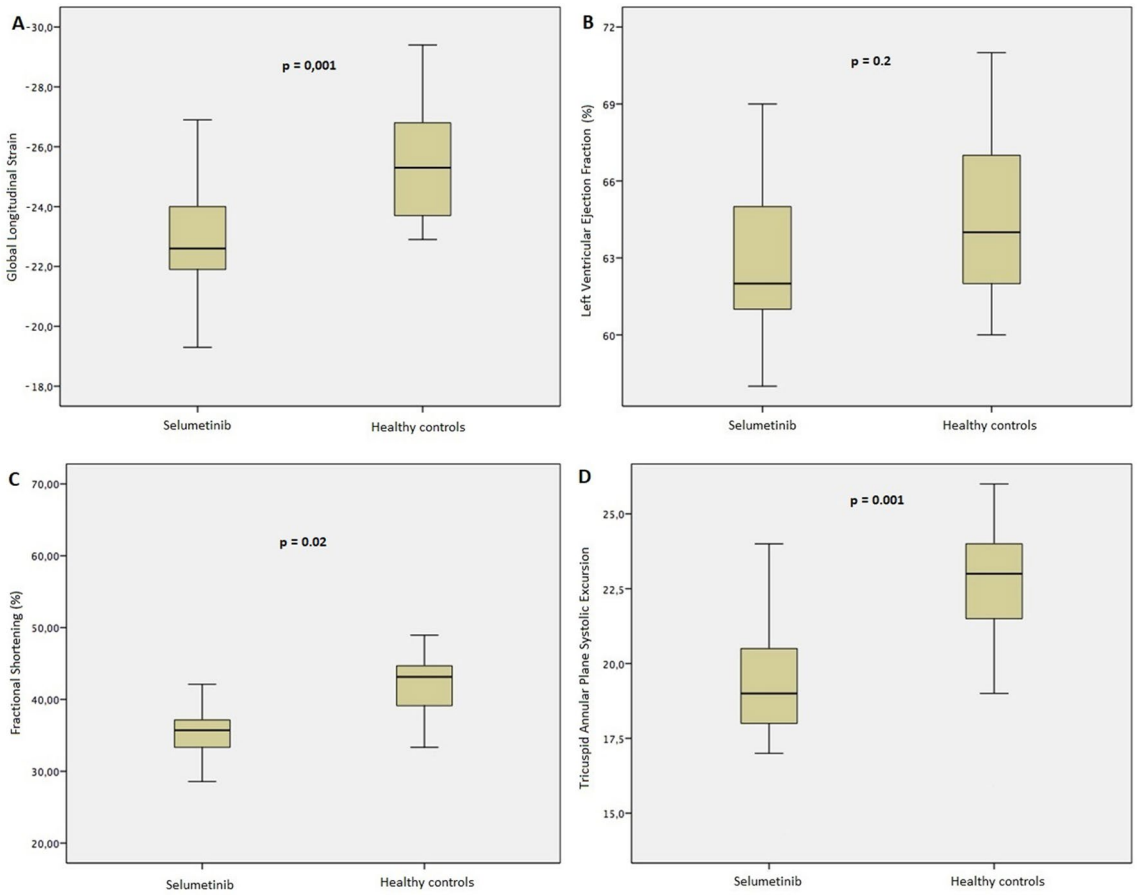

Fig. 1 Box plot depicts the difference between patients with neurofibromatosis type 1 treated with selumetinib and healthy controls in the mean value of global longitudinal strain (**A**), left ventricular ejection fraction (**B**), fractional shortening (**C**) and tricuspid annular plane systolic excursion

Table 2 GLS values according to the length of selumetinib treatment

LoT (months)	GLS when treated < LoT	GLS when treated > LoT	*p*-Value
4	23 ± 1	23 ± 2	0.84
6	23 ± 1	23 ± 2	0.93
12	22 ± 1	23 ± 2	0.41
24	23 ± 2	23 ± 2	0.9
36	23 ± 2	22 ± 1	0.54

Values are given as mean ± standard deviation

GLS global longitudinal strain, *LoT* length of treatment

Table 3 Side effects of selumetinib in the study cohort

Side effects	*n* (%)
Total	12 (71%)
Gastrointestinal toxicity	5 (29%)
Dermatologic toxicity	9 (53%)
Creatine phosphokinase elevations	7 (41%)
Other side effects	3 (18%)

Values are given as *n* (%)

during treatment with selumetinib after five cycles (28-day cycles). Administration of selumetinib was then suspended, and treatment with lisinopril was prescribed. Left ventricular ejection fraction returned to 55% within 3 months. Selumetinib was finally resumed at a reduced dose with regular monitoring of LVEF, which remained normal.

Furthermore, in another study [8], one patient discontinued selumetinib permanently after 168 days because of worsening LVEF and a lack of clear benefit for PNs. Restoration of normal LVEF was achieved within a month from therapy discontinuation.

Currently, patients treated with selumetinib are regularly monitored (i.e. every 4 months) with a complete cardiac evaluation including echocardiography, with an accurate

assessment of cardiac function, which is performed according to LVEF values measured by the Simpson biplane method. However, breaking down the essential components of cardiac contraction, deformation imaging such as speckle-tracking echocardiography has been demonstrated more accurate than LVEF in the evaluation of systolic function [19, 20, 28].

In recent years, GLS has been increasingly recognised as a reliable methodology to assess chemotherapy-related cardiotoxicity in patients with cancer [20]. Moreover, it has been recently included in the guidelines of some paediatric consensuses supporting its clinical application for this specific purpose [20, 29].

To our best knowledge, this is the first study in the literature investigating the possible use of GLS measurement to assess systolic function in patients with NF1 being treated with selumetinib. This patient cohort has been already described in a previous paper in terms of the effectiveness and safety of selumetinib [6] showing a tumour reduction of $>20\%$ in 94% of children treated, with some patients achieving remarkable functional and aesthetic results. Of note, the study cohort was compared with a control group of healthy peers, matched by sex and age, and a cohort of patients with untreated NF1.

Our findings suggest that GLS and fractional shortening could reveal subtle changes in cardiac function in patients with NF1 treated with selumetinib, not adequately identified by LVEF. These findings have never been shown before and deserve attention, potentially having major clinical implications for the monitoring of cardiac function and early identification of subtle changes in cardiac contractility among patients with NF1 during treatment with selumetinib.

5 GLS in the Evaluation of Cardiac Function in Patients with NF1

In 2020, a study [23] showed statistically significant differences in GLS values between a cohort of 22 patients affected by NF1 and a control group of healthy peers. In detail, the average GLS values were lower in patients with NF1 compared with controls while remaining within the normal range in most patients ($-19.3 \pm 1.7\%$ vs -21.5 ± 2.7, respectively; $p = 0.008$). In the present study, we included a cohort of 17 patients with untreated NF1. Although they could not be matched by sex and age with the study group, no difference emerged in GLS values among these two populations ($-25.2 \pm 2\%$ vs $-25.5 \pm 2\%$, $p = 0.65$). Whilst the study by Cutruzzolà et al. reported impaired GLS values in 18% of patients (according to the reference ranges), this was not found in our study, despite three patients having borderline/low-normal GLS values according to reference values published by Levy et al. [25].

Furthermore, in the present study, no association was found between lower GLS values and the duration of selumetinib treatment, analysed at different time intervals. In addition, similar GLS values were found among 12 patients who experienced other drug-related side effects and those five who did not.

Therefore, the findings of this study suggest the possible occurrence of subtle changes in systolic function reflected by lower GLS values (still within the normal limits) in patients with NF1 treated with selumetinib, regardless of the time from treatment initiation. Our results support the use of a strain analysis with GLS to monitor cardiac function in patients being treated with possible cardiotoxic drugs. As previously suggested in other conditions [29, 30], GLS could be a part of a screening protocol in the cardio-oncology field in order to identify early changes in cardiac function, possibly related to cardiotoxicity, allowing prompt initiation of specific therapy (i.e., beta-blockers, ACE inhibitors, statins or iron chelators) before a decline in LVEF [30–33]. Although initial, the findings of the present might pave the way for further dedicated studies in this field investigating the possible clinical application of GLS for monitoring cardiac function in the paediatric population of patients with NF1 treated with selumetinib.

6 Limitations of the Study

Although this was a single-centre retrospective analysis on a small cohort, the present study is the first in the literature characterising cardiac function by GLS measurement in patients with NF1 treated with selumetinib and providing evidence for a possible clinical use of GLS in the identification of subtle changes in systolic function, not accurately revealed by LVEF. Of note, a longitudinal evaluation of GLS values from the diagnosis of NF1 in this population would have provided more insights into the possible changes in cardiac function following initiation of selumetinib. For this reason, we could not evaluate the changes in GLS values over time, which has been demonstrated to be a more solid parameter compared with the absolute GLS value [34]. Finally, these are initial findings of this study and require further dedicated research.

7 Conclusions

Patients with NF1 treated with selumetinib may experience subtle changes in systolic function identified by GLS and not revealed by LVEF. Global longitudinal strain might be useful to monitor cardiac function in this cohort of patients for the duration of therapy. Whether these changes reflect

selumetinib-related cardiotoxicity will require future dedicated research.

Declarations

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Conflicts of Interest Thomas Caiffa, Antimo Tessitore, Andrea Magnolato, Matilde Petz, Marco Bobbo, Daniela Chicco, Biancamaria D'Agata Mottolese, Aldostefano Porcari, Egidio Barbi, Gianfranco Sinagra and Irene Bruno have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval Ethics committee approval was not requested according to the Italian Law (Authorization no. 9/2014).

Consent to Participate We received informed consent from the patients' parents and the patients themselves.

Consent for Publication We received informed consent from the patients' parents and the patients themselves.

Availability of Data and Material All relevant data are included in the article and/or its supplementary information files. All other data supporting the study (such as radiological photos or images) are available from the corresponding author upon request.

Code Availability Not applicable.

Authors' Contributions AT and TC wrote the first draft of the manuscript. TC, MB, DC and BDAM collected and processed the data. MP reviewed the literature. EB, AM, IB, AP and GS critically revised the manuscript for relevant intellectual content. All authors read and approved the final manuscript.

References

1. Jafry M, Sidbury R. RASopathies. Clin Dermatol. 2020;38(4):455–61.
2. Dombi E, Baldwin A, Marcus LJ, Fisher MJ, Weiss B, Kim A, et al. Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas. N Engl J Med. 2016;375(26):2550–60.
3. Jensen SE, Patel ZS, Listernick R, Charrow J, Lai JS. Lifespan development: symptoms experienced by individuals with neurofibromatosis type 1 associated plexiform neurofibromas from childhood into adulthood. J Clin Psychol Med Settings. 2019;26(3):259–70.
4. Gross AM, Singh G, Akshintala S, Baldwin A, Dombi E, Ukwuani S, et al. Association of plexiform neurofibroma volume changes and development of clinical morbidities in neurofibromatosis 1. Neuro Oncol. 2018;20(12):1643–51.
5. Gross AM, Wolters PL, Dombi E, Baldwin A, Whitcomb P, Fisher MJ, et al. Selumetinib in children with inoperable plexiform neurofibromas. N Engl J Med. 2020;382(15):1430–42.
6. Baldo F, Grasso AGG, Cortellazzo Wiel L, Maestro A, Trojniak MP, Murru FM, et al. Selumetinib in the treatment of symptomatic intractable plexiform neurofibromas in neurofibromatosis type 1: a prospective case series with emphasis on side effects. Pediatr Drugs. 2020;22(4):417–23.
7. Passos J, Nzwalo H, Azevedo M, Tavares M, Nunes S. Dramatic improvement of a massive plexiform neurofibroma after administration of selumetinib. Pediatr Neurol. 2020;105:69–70.
8. Espírito Santo V, Passos J, Nzwalo H, Carvalho I, Santos F, Martins C, et al. Selumetinib for plexiform neurofibromas in neurofibromatosis type 1: a single-institution experience. J Neurooncol. 2020;147(2):459–63.
9. Jackson S, Baker EH, Gross AM, Whitcomb P, Baldwin A, Derdak J, et al. The MEK inhibitor selumetinib reduces spinal neurofibroma burden in patients with NF1 and plexiform neurofibromas. Neurooncol Adv. 2020;2(1):95.
10. Harder A. MEK inhibitors: novel targeted therapies of neurofibromatosis associated benign and malignant lesions. Biomark Res. 2021;9(1):1–9.
11. Weiss BD, Wolters PL, Plotkin SR, Widemann BC, Tonsgard JH, Blakeley J, et al. NF106: a neurofibromatosis clinical trials consortium phase II trial of the MEK inhibitor mirdametinib (PD-0325901) in adolescents and adults with NF1-related plexiform neurofibromas. J Clin Oncol. 2021;39(7):797–806.
12. Fisher MJ, Shih CS, Rhodes SD, Armstrong AE, Wolters PL, Dombi E, et al. Cabozantinib for neurofibromatosis type 1–related plexiform neurofibromas: a phase 2 trial. Nat Med. 2021;27(1):165–73.
13. Robertson KA, Nalepa G, Yang FC, Bowers DC, Ho CY, Hutchins GD, et al. Imatinib mesylate for plexiform neurofibromas in patients with neurofibromatosis type 1: a phase 2 trial. Lancet Oncol. 2012;13(12):1218–24.
14. Jakacki RI, Dombi E, Steinberg SM, Goldman S, Kieran MW, Ullrich NJ, et al. Phase II trial of pegylated interferon alfa-2b in young patients with neurofibromatosis type 1 and unresectable plexiform neurofibromas. Neuro Oncol. 2017;19(2):289–97.
15. Hwang J, Mang YH, Lee BH, Hwa KP, Kim KW. Efficacy and safety of selumetinib in pediatric patients with neurofibromatosis type 1: a systematic review and meta-analysis. Neurology. 2022;98(9):e938–46.
16. Abdel-Rahman O, ElHalawani H, Ahmed H. Risk of selected cardiovascular toxicities in patients with cancer treated with MEK inhibitors: a comparative systematic review and meta-analysis. J Glob Oncol. 2015;1(2):73–82.
17. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/industry task force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging. 2015;16(1):1–11.
18. Cameli M, Mondillo S, Galderisi M, Mandoli GE, Ballo P, Nistri S, et al. Speckle tracking echocardiography: a practical guide. G Ital Cardiol. 2017;18(4):253–69.
19. Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. JACC Cardiovasc Imaging. 2018;11(2):260–74.
20. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol. 2014;63(25):2751–68.
21. Legius E, Messiaen L, Wolkenstein P, Pancza P, Avery RA, Berman Y, et al. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. Genet Med. 2021;23(8):1506–13.
22. Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol. 1988;45:575–8.

23. Cutruzzolà A, Irace C, Frazzetto M, Sabatino J, Gullace R, De Rosa S, et al. Functional and morphological cardiovascular alterations associated with neurofibromatosis 1. Sci Rep. 2020;10(1):1–9.
24. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr. 2010;23(5):465–95.
25. Levy PT, Machefsky A, Sanchez AA, Patel MD, Rogal S, Fowler S, et al. Reference ranges of left ventricular strain measures by two-dimensional speckle-tracking echocardiography in children: a systematic review and meta-analysis. J Am Soc Echocardiogr. 2016;29(3):209-25.e6.
26. General Authorisation to Process Personal Data for Scientific Research Purposes. Deliberated March 1, 2012. *Gazzetta Ufficiale della Repubblica Italiana*. n. 72. Published March 26, 2012. Accessed August 2, 2012.
27. Robert C, Dummer R, Gutzmer R, Lorigan P, Kim KB, Nyakas M, et al. Selumetinib plus dacarbazine versus placebo plus dacarbazine as first-line treatment for BRAF-mutant metastatic melanoma: a phase 2 double-blind randomised study. Lancet Oncol. 2013;14(8):733–40.
28. Buckberg G, Hoffman JIE, Mahajan A, Saleh S, Coghlan C. Cardiac mechanics revisited: the relationship of cardiac architecture to ventricular function. Circulation. 2008;118(24):2571–87.
29. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2014;27(9):911–39.
30. Kalam K, Marwick TH. Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: a systematic review and meta-analysis. Eur J Cancer. 2013;49(13):2900–9.
31. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol. 2010;55(3):213–20.
32. Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. J Clin Oncol. 2010;28(25):3910–6.
33. Negishi T, Negishi K, Agler D, Plana J, Haluska B, Marwick T. Cardio-protective effect of beta-blockade during chemotherapy for breast cancer. J Am Coll Cardiol. 2012;59(13):E1248.
34. Negishi K, Negishi T, Hare JL, Haluska BA, Plana JC, Marwick TH. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. J Am Soc Echocardiogr. 2013;26(5):493–8.