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Title of Project: To see the early effect of sorafenib on cognition, cardiovascular, and reproductive functions in patients with fibromatosis

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ABSTRACT

INTRODUCTION: Sorafenib, a multi tyrosine kinase inhibitor has proven to be a promising drug for treating fibromatosis. However, there is no upper limit for sorafenib duration and is continued indefinitely. The prolonged use of sorafenib may lead to cognitive impairment, cardiovascular-related abnormalities, and reproductive dysfunction. This study aims to assess these factors prospectively.

METHODOLOGY: This is a prospective longitudinal study ongoing at AIIMS, New Delhi (funded by DTRF) in patients with fibromatosis and age >18 years in which sorafenib is being started. Cardiac and vascular function tests are being done at four time points baseline, 3, 6, and 12 months. Troponin I and BNP are measured by chemiluminescent microparticles (CMIA). Echocardiographic evaluation is being done for the assessment of global longitudinal strain and left ventricular ejection fraction (by Simpson's method). Blood pressure measurements were done monthly and fasting lipid profile (LP) are measured routinely at baseline, 3, 6, and 12 months follow-up. Assessment of carotid-femoral pulse wave velocity (PWV), aortic augmentation index (AI) is being done by SPHYGMOCORE device and carotid beta stiffness index (CBSI) by ARTSENS plus device. Carotid intima-media thickness (CIMT) and endothelial function by flow mediated dilatation (FMD) is acquired and being analysed. and Cognitive function is tested at three time points; baseline, 6 months, and 12 months. Questionnaire-based subjective assessment was done using Functional Assessment of Cancer Therapy-Cognition Version 3 (FACT-Cog V3), Depression Anxiety and Stress Questionnaire-21 (DASS-21), and Appearance Anxiety Inventory (AAI). The objective cognitive assessment is being done by using a computer-based Cambridge Neuropsychological Test Automated Battery (CANTAB) for the neuropsychological tests (processing and psychomotor speed, attention and short-term visual memory, working memory and strategy, sensorimotor function, and comprehension). Endocrine and reproductive function hormone analysis is being done at three time points; baseline, 6 months, and 12 months. Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Estrogen (E2), Anti-Mullerian Hormone (AMH), and Thyroid Stimulating Hormone (TSH) are measured using CMIA [Refer to Table 1]. Statistical analysis was done using GraphPad Prism. Repeated ANOVA or its non-parametric variants was used for analysis for groups across the different time points. Multiple comparison was done to compare each group against the other group. Mixed-effect analysis was done to analyze the group with missing data.

RESULTS: This study was started in September 2023. A total of 21 participants have been enrolled in the study and 52% were male. The median age of the participants was 32 years. The median

duration of sorafenib was 8 months (range:1-11 months) with a median dose of 200 mg (range:200-400). There was a statistically significant decrease in CBSI at baseline vs. 3 months; p-value: 0.0359. The rest of the cardiovascular parameters; PWV, AI, LP, BNP, and Troponin I, were comparable (p-value: ns) across the time points. The blood pressure p-value: ns; however, 4 patients were started on hypotensive drugs due to grade 1 hypertension. The mean global longitudinal strain and left ventricle ejection fraction were (-15.5%) and 61.295 respectively at baseline. The results obtained during cognitive and neuropsychological assessment showed no significant difference between baseline and 6 months across subjective (FACT-Cog) and objective parameters (CANTAB tests). Further, the scores for depression, anxiety, and stress, using DASS 21 and AAI showed comparable results of baseline versus 6 months. The hormone profile showed a significant increase in serum TSH level with a p-value: 0.04. In all patients, there is no change in troponin I levels except for two patients 469 pg/mL at 3 months and 1217.6 pg/mL at 6 months follow-up respectively. All BNP values were within the normal range before and after 6 months of the start of sorafenib. Baseline MRI brain is normal for all the patients enrolled so far.

CONCLUSION: As per the interim report, it is observed that there is significant hypothyroidism in patients and non-significant increase in blood pressure (though 4 patients were started on anti hypertensive for Gr 1 hypertension). However, the study is being going on for longer follow-up to detect any toxic reaction due to sorafenib.

Table1:

	Parameters assessed	**Number of patients tested at each time point**			
		Baseline	**3 months**	**6 months**	**12 months**
Vascular functions	Local and regional measures of arterial stiffness				
	● Carotid femoral pulse wave velocity (cf PWV)	18	17	12	
	● Carotid artery beta stiffness index (CBSI)*	12	15	11	
	● Aortic Augmentation index (AI)	18	17	12	

	Endothelial function ● Brachial artery flow-mediated dilatation	Data has been acquired and is being analysed			
	Sub-clinical atherosclerotic change in the carotid artery ● Carotid intima-media thickness	Data has been acquired and is being analysed			
Cognitive functions	Subjective assessment ● Fact Cog Questionnaire ● DASS-21 Questionnaire ● AAI Questionnaire	 18 19 19		 12 12 12	
	Objective assessment using CANTAB for the following domains: Attention, Working memory, Processing speed	20		12	
	Neuroimaging: MRI Brain	18			
Cardiac Functions	BP monitoring	19	17	12	
	Echocardiography ● Measurement of left ventricular function · Calculation of EF by Simpson's ● Calculation of global longitudinal strain	 19 19			
	Fasting lipid profile	20	17	12	

	Cardiac biomarkers for myocardial injury and heart failure ● Troponin I ● BNP	 20 20	 16 16	 11 11	
Endocrinal and reproductive	● TSH ● LH ● FSH ● AMH ● E2	19 19 19 19 19		12 12 12 12 12	

*Carotid beta stiffness index (CBSI) measurements could not be performed on the patients where the artery was superficial and the quality of the echo signal was low.