IMPACT OF SARCOPENIA ON EFFICACY AND TOXICITY PROFILE OF CDK4/6 INHIBITORS IN METASTATIC BREAST CANCER PATIENTS: A REAL-WORLD ANALYSIS

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Abstract

CDK4/6 inhibitors (CDK4/6i) combined with endocrine therapy are standard first-line treatment in HR+/HER2- metastatic breast cancer (mBC). Sarcopenia is prevalent in cancer patients and has been linked to poorer outcomes and higher toxicity, but its role in patients treated with CDK4/6 inhibitors remains under-investigated. This real-world retrospective study aims to evaluate the impact of sarcopenia on survival outcomes (progression-free survival [PFS] and overall survival [OS]) and toxicity in mBC patients receiving CDK4/6i.

Characteristics	Pts (N=75)
Age – yr	
Median	58
Menopausal status	**N (%)**
Postmenopausal	53 (71)
Premenopausal	22 (29)
BMI	**N (%)**
<18.5	1 (1)
18.5-24.9	51 (68)
25-29.9	14 (19)
>30	9 (12)
CDK4/6	**N (%)**
Palbociclib	33 (44)
Ribociclib	40 (53)
Abemaciclib	22 (7)
ET companion	**N (%)**
Aromatase Inhibitors	41 (55)
Fulvestrant	34 (45)

Table 1. Population characteristics.

Methods and Materials

A retrospective analysis was conducted on clinical data of patients with histologically confirmed HR+/HER2– stage IV mBC at Sant'Andrea University Hospital. All patients had de novo metastatic or relapsed disease treated with first-line CDK4/6i plus endocrine therapy (ET). Sarcopenia was assessed using CT scans performed at baseline before treatment initiation,
with the third lumbar vertebra (L3) as the reference point. Body composition analysis was performed using artificial intelligence-based automatic segmentation software (DeepCatch). The skeletal muscle index (SMI) cutoff value of 38.5 cm^2/m^2 was used to classify patients as sarcopenic or non-sarcopenic. Statistical analyses included univariate and multivariate analyses using Cox proportional hazards models and Kaplan-Meier survival curves.

Results

The cohort (Table 1) included 75 mBC patients with a median age of 58 years; 53 were postmenopausal, 22 premenopausal. BMI distribution: 1 underweight (BMI < 18.5), 51 normal weight (18.5–24.9), 14 overweight (25–29.9), and 9 obese (≥30). Regarding treatment, 33 received palbociclib, 40 received ribociclib, and 2 received abemaciclib. ET companion included aromatase inhibitors (n=41) or fulvestrant (n=34). Any grade toxicity occurred in 34 patients (45%), with G3/4 events in 23 cases (31%). Best responses were detected as following: 3 complete response (CR), 29 partial response (PR), 31 stable disease (SD), and 12 progression disease (PD). Overall, 42 patients (56%) were classified as sarcopenic. 17 patients (23%) had bone-only disease while 58 patients (77%) presented with visceral metastases. Median PFS was 27 months in sarcopenic patients versus 23 months in non-sarcopenic patients (HR=0.79, p=0.4684). Median OS was 51 months versus 47 months, respectively (HR=0.672, p=0.2721). No statistically significant differences were observed in survival outcomes between sarcopenic and non-sarcopenic patients.

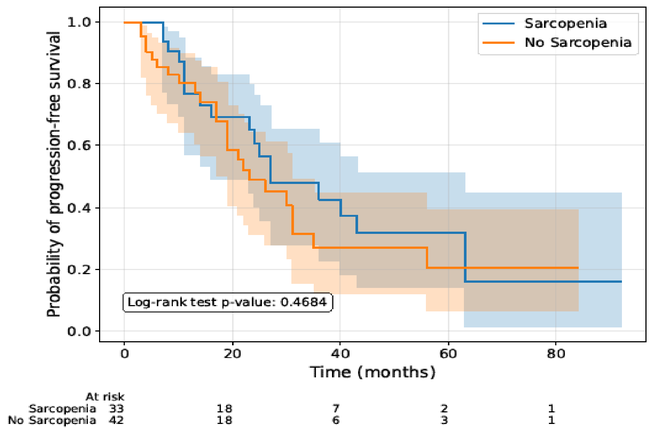


Figure 1. PFS in sarcopenic patients vs. non-sarcopenic patients

Results (2nd part)

Significant associations were identified between sarcopenia and severe toxicity (G3/4): 61% of patients with severe toxicity were sarcopenic compared to 37% with mild-moderate toxicity (p=0.05). Notably, while BMI categorized into standard classes showed no significant correlation with sarcopenia (p=0.08), BMI as a continuous variable demonstrated superior discriminatory ability, showing a significant protective effect against sarcopenia (OR=0.798, 95% CI: 0.668-0.955, p=0.010). Each unit increase in BMI was associated with a 20% reduction in the odds of sarcopenia, and sarcopenic patients had a lower mean BMI (23.0 vs 25.8 kg/m^2, p=0.003). No significant associations were found with type of CDK4/6i, age, menopausal status, or bone-only vs. visceral disease (p> 0.05). Multivariate analysis confirmed BMI as a continuous variable (p=0.010) and severe toxicity grading (p=0.046, OR=3.118) as independent predictive factors for sarcopenia.

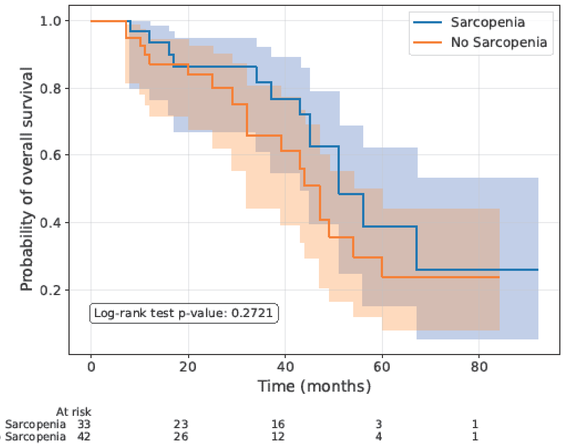


Figure 2. OS in sarcopenic patients vs. non-sarcopenic patients

Conclusions

In conclusion, within our cohort of mBC patients treated with first-line CDK4/6i and endocrine therapy, the presence of sarcopenia did not appear to represent a negative prognostic factor associated with poorer overall survival or progression-free survival outcomes. However, BMI and severe toxicity emerged as independent predictors of sarcopenia. The significant association between sarcopenia and G3/4 toxicity suggests the need for nutritional screening and closer monitoring of sarcopenic patients to optimize treatment tolerability. These findings support the implementation of body composition assessment in clinical practice for patients receiving CDK4/6i plus ET. Further research is warranted to deepen the investigation of these findings.

Parameters		No Sarcopenia	Sarcopenia	Total	p-value
Age	<65	24	20	44	0,762
	>65	18	13	31	
BMI	<18.5	0	1	1	0,085
	18,5-24,9	25	26	51	
	25-29,9	9	5	14	
	≥30	8	1	9	
Menopausal status	Postmenopausal	30	23	53	0,870
	Premenopausal	12	10	22	
CDK4/6i	Palbociclib	19	14	33	0,961
	Ribociclib	22	18	40	
	Abemaciclib	1	1	2	
ET companion	IA	27	14	41	0,059
	Fulvestrant	15	19	34	
Tox any grade	No	25	16	41	0,340
	Yes	17	17	34	
Grade max tox	G1-G2	33	19	52	0,050
	G3-G4	9	14	23	
Best response	RC	0	3	3	0,133
	RP	16	13	29	
	SD	17	14	31	
	PD	9	3	12	
Dose reduction	No	26	18	44	0,521
	Yes	16	15	31	
Bone only	No	30	28	58	0,168
	Yes	12	5	17	
Visceral disease	No	12	5	17	
	Yes	30	28	58	

Table 2. Univariate analysis

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