Sarcopenia and acute severe toxicity in sarcoma patients treated with doxorubicin-based chemotherapy

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Abstract

Aim

Lean body mass (LBM) better than body surface area (BSA), predicts the clearance and toxicity of epirubicin in breast cancer patients (pts) (Prado et al, 2010). Since the dose-intensity of anthracycline-based chemotherapy may be critical in sarcoma pts, we studied whether sarcopenia was associated with the occurrence of acute severe toxicity in this population.

Methods

Sarcoma pts treated with doxorubicin-based chemotherapy and having a CT scan including the 3rd lumbar vertebrae prior chemotherapy were selected. Skeletal muscle cross-sectional area were measured and sarcopenia was defined using standardized thresholds (Antoun et al, 2010). Acute severe toxicity was defined as any grade 4 toxicity or febrile neutropenia (FN) or grade ≥ 3 gastrointestinal (GI) toxicity, according to the NCI-CTC occurring at 1st cycle. Sarcopenic and non-sarcopenic pts were compared (chi-2 test or Fischer's exact test for qualitative data).

Results

42 consecutive soft tissue (n=24; 57%) and bone sarcoma (n=18; 43%) pts were eligible (57.1% males, median age 48 yrs, range 22-68), and received a median doxorubicin dose of 112 mg at first cycle (range 84-148). At baseline, 24 pts (57.1%) were sarcopenic. A normal body mass index (BMI) was found in 13 (54%) of the sarcopenic patients, 11 (46%) were overweighted. During the first cycle, acute severe toxicity were hematologic (11 pts 26.2%), FN (8 pts 19.0%), and GI (6 pts 14.3%). Sarcopenic pts had significantly more acute severe toxicity (11/24 versus 3/18, p=0.04), more grade 4 hematotoxicity (9/24 versus 2/18, p=0.05), more FN (7/24 versus 1/18, p=0.05). Pts with sarcopenia and BMI< 25 kg/m2 experienced significantly more grade ≥3 GI toxicity (4/13 versus 2/29, p=0.04).

Conclusions

Sarcopenia in sarcoma patients is associated with high-risk of acute severe toxicity.

Background

- Sarcoma are rare malignant tumors. Chemotherapy based on doxorubicin, alone or in combination, is the cornerstone of medical treatment. Hematologic toxicity, stomatitis and nausea-emesis represent the most frequent acute toxicities, susceptible to reduce dose-intensity.
- Lean body mass (LBM), better than BSA, had been shown to predict clearance of epirubicin and correlated to toxicity in women with breast cancer.
- Sarcopenia is the condition of low muscle mass, with specific cut off established in cancer patients. Measure of muscle mass can be assessed on Computer Tomography images.
- We hypothesized that sarcopenia could help to identify sarcoma patients susceptible to experience doxorubicin acute severe toxicity.

Patients and methods

A retrospective study on patient's charts

- sarcomas patients
- treated with doxorubicin-based chemotherapy in the medical oncology department of Cochin hospital, Paris, France.
- CT scan 30 days before treatment

Treatment and toxicity assessment

- For neo-AI, AI and API-AI protocol, doxorubicin dose was 60 mg/m² and 75 or 80 mg/m² for doxorubicin high dose protocol
- Grade ≥ 3 toxicities were assessed at each cycle, every 2 or 3 weeks, according to protocol
- Acute severe toxicity was defined as grade 4 hematological toxicity, febrile neutropenia (FN) or grade ≥ 3 gastrointestinal (GI) toxicity, according to the NCI-CTC occurring at 1st cycle

Images analysis

- Total lean body mass (LBM) was estimated from L3 skeletal muscle cross-sectional areas according to the following equation: LBM (kg) =0.30(skeletal muscle area at L3 using CT (cm2))+ 6.06)
- The sex-specific cutoff values for sarcopenia were 55.4 cm²/m² for males and 38.9 cm²/m² for females (Antoun *et al*, 2010)

Statistical analysis

Prevalence of toxicity was compared using chi-2 or Fisher's exact test, and Mann–Whitney's test was used for the comparison of continuous variables. All P-values were two-sided, and the level of significance was P ≤0.05.

Results

Table 1. Baseline characteristics

	Men, n=29	Women, n=18	Total, n=47
Age, median (range)	48 (28 ; 68)	46,5 (17 ; 65)	48 (17 ; 68)
ECOG PS, n (%)			
0-1	23 (79)	15 (83)	38 (81)
≥ 2	6 (21)	3 (17)	9 (19)
Weight (kg), median (range)	79 (56 ; 130)	61,5 (48 ; 95)	73 (48 ; 130)
Lean Body Mass (kg), median (range)	53,5 (34,8 ; 67,5)	38,6 (27,7 ; 43,5)	47,2 (28,2 ; 67,2)
Sarcopenia, n (%)	23 (79)	7 (39)	30 (64)
Sarcopenia + BMI < 25, n (%)	10 (34)	6 (33)	17 (36)
Anatomo pathology, n (%)			
Osteosarcoma	4 (14)	6 (33)	10 (21)
Ewing sarcoma	1 (3)	3 (17)	4 (9)
Synovialosarcoma	2 (7)	3 (17)	5 (11)
Leiomyosarcoma	1 (3)	4 (22)	5 (11)
Dedifferentiated Liposarcoma	3 (10)	0 (0)	3 (6)
Unclassified	16 (55)	1 (5.5)	17 (36)
Others	2 (7)	1 (5.5)	3 (6)
Extension, n (%)			
Local	21 (72)	10 (56)	31 (66)
Locally advanced and metastatic	8 (28)	8 (44)	16 (34)
Albumin (g/L), n (%)			
> 35	21 (78)	15 (94)	36 (84)
30-35	3 (11)	0 (0)	3 (7)
<30	3 (11)	1 (6)	4 (9)
Chemotherapy			
Neo AI	6 (21)	6 (33)	12 (26)
AI	11 (37)	2 (11)	13 (27)
API-AI	10 (34)	7 (39)	17 (36)
High dose Doxorucin	2 (7)	3 (17)	5 (11)

Abbreviations: ECOG PS Eastern Cooperative Oncology Group performance status; BMI= body mass index (weight/height²)

Table 2. Toxicity and sarcopenia

Toxicity of interest during first cycle	No sarcopenia n=17	Sarcopenia n=30	P
Febrile neutropenia, n (%)	1 (5.8)	7 (23.3)	0.228*
Hematologic toxicity ≥ grade 4, n (%)	1 (5.8)	10 (33.3)	**0.039***
Gastro-intestinal toxicity ≥ grade 3, n(%)	2 (11.8)	4 (13.3)	1*
Anemia ≥ grade IV, n (%)	0 (0)	1 (3.3)	1*
Thrombopenia ≥ grade III, n (%)	1 (5.8)	3 (10)	1*
Acute Severe Toxicity, n (%)	2 (11.8)	12 (40)	**0.041**

* non parametric test

- Sarcopenia has a high prevalence among sarcoma patients
- Sarcopenic patients are at higher risk of hematologic toxicity and acute severe toxicity during first cycle

Table 3 and 4. Anthropometric and biologic measurements in patients with and without acute severe toxicity

	Acute severe toxicity	No severe toxicity	P
FEMALES, mean (SD)	**n=6**	**n=12**	
Age (years)	52 (16)	41 (14)	0,15
Height (m)	1,57 (0,06)	1,62 (0,05)	0,06
Weight (kg)	60,8 (14,1)	68,2 (13,3)	0,29
Body Mass Index (kg/m²)	24,5 (4,8)	26,1 (6,2)	0,60
Lean Body Mass (kg)	35,0 (6,4)	39,2 (2,7)	0,06
Skeletal Muscle L3 index (cm/m²)	37,9 (7,1)	42,1 (3,4)	0,11
Body Surface Area (m²)	1,6 (0,2)	1,7 (0,2)	0,17
Sarcopenia, n (%)	4 (66)	3 (25)	0,14*
MALES, mean (SD)	**n=8**	**n=21**	
Age (years)	51 (13)	48 (10)	0,43
Height (m)	1,7 (0,1)	1,8 (0,1)	0,38
Weight (kg)	76,9 (11,9)	80,0 (15,3)	0,62
Body Mass Index (kg/m²)	25,1 (3,4)	25,4 (3,6)	0,88
Lean Body Mass (kg)	52,1 (4,2)	53,9 (7,7)	0,54
Skeletal Muscle L3 index (cm/m²)	49,2 (2,8)	50,5 (7,7)	0,65
Body Surface Area (m²)	1,9 (0,2)	2,0 (0,2)	0,57
Sarcopenia, n (%)	8 (100)	15 (72)	0,15*

*non parametric test

Mean (SD)	Acute severe toxicity n=14	No severe toxicity n=33	P
Age (years)	52 (13)	45 (12)	0,12
Height (m)	1,7 (0,1)	1,7 (0,1)	0,15
Weight (kg)	70,0 (14,8)	75,6 (15,4)	0,25
Body Mass Index (kg/m²)	24,9(3,9)	25,6(4,6)	0,60
Lean Body Mass (kg)	44,7 (10,1)	48,5 (9,2)	0,23
Skeletal Muscle L3 index (cm/m²)	44,3 (7,6)	44,8(7,6)	0,20
Body Surface Area (m²)	1,8 (0,2)	1,9 (0,2)	0,19
Sarcopenia, n (%)	12 (85)	18 (55)	**0,04**
ECOG PS			
0-1	10	28	0,72
≥2	14	33	
Age (years)			
<60	8	30	**0,01***
≥60	6	3	
Disease extension			
Local	10	21	0,50*
LA / Metastatic	3	12	
Albumin (g/L)			
>35	10	26	0,66*
<35	3	4	
CRP (mg/l)			
Normal	7	18	0,53
> Normal	7	12	

*non parametric test
Abbrevations ECOG PS Eastern Cooperative Oncology Group performance status
LA: Locally Advanced

Conclusion

- The prevalence of sarcopenia appears important in this population with 64% of the patients being sarcopenic before treatment
- In our study, sarcopenic sarcoma patients were at high risk of developing acute severe toxicities during first cycle of doxorubicin-based chemotherapy defined as any grade 4 hematological toxicity, febrile neutropenia or grade ≥ 3 gastrointestinal toxicity
- The main limitations of our study are its retrospective nature, the small number of patients included and the heterogeneity of our population
- These results are in line with those previously reported by V. Baracos

References

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