BRIEF REPORT

Predictive value of skeletal muscle mass for immunotherapy with nivolumab in non-small cell lung cancer patients: A "hypothesis-generator" preliminary report

Alessio Cortellini[1,2] 🆔, Lucilla Verna[2], Giampiero Porzio[1,2], Federico Bozzetti[3], Pierpaolo Palumbo[2], Carlo Masciocchi[2], Katia Cannita[2], Alessandro Parisi[1,2], Davide Brocco[4], Nicola Tinari[5] & Corrado Ficorella[1,2]

1 Medical Oncology, San Salvatore Hospital, University of L'Aquila, L'Aquila, Italy
2 Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy
3 Faculty of Medicine, University of Milan, Milan, Italy
4 Clinical Oncology Unit, S.S. Annunziata Hospital, Chieti, Italy
5 Department of Medical, Oral and Biotechnological Sciences, University G. D'Annunzio, Chieti, Italy

Abstract

Sarcopenia represents one of the hallmarks of all chronic disease, including non-small cell lung cancer (NSCLC). A computed tomography scan is an easy modality to estimate the skeletal muscle mass through cross-sectional image analysis at the level of the third lumbar vertebra (L3). Baseline skeletal muscle mass (SMM) was evaluated using gender-specific cutoffs for skeletal muscle index in NSCLC patients administered immunotherapy with nivolumab to evaluate its possible correlations with clinical outcomes. From April 2015 to August 2018, 23 stage IV NSCLC patients were eligible for image analysis. Nine patients (39.1%) had low SMM. Among patients with baseline low and non-low SMM, median progression free survival was 3.1 and 3.8 months, respectively ($P = 0.0560$), while median overall survival was 4.1 and 13 months, respectively ($P = 0.2866$). This hypothesis-generating preliminary report offers the opportunity to speculate about the negative influence of sarcopenia on immune response. In our opinion, nutritional status could affect the clinical outcomes of immunotherapy, even if we cannot make definitive conclusions here. Further studies on the topic are required.

Introduction

Sarcopenia is a condition that causes the loss of muscle mass and decreased muscle power. It is a para-physiologic event that occurs during aging, but represents one of the hallmarks of all chronic disease, including cancer. Sarcopenia develops in approximately 50% of advanced cancer patients and is related to malnutrition, inflammation, and treatments. It creates a "vicious circle" that negatively affects most clinical outcomes, such as toxicity and survival.[1] A recent study reported that 55.8% of resected non-small cell lung cancer (NSCLC) patients present with sarcopenia,[2] indicating that things could be worse in the metastatic setting.

Almost every NSCLC patient undergoes a routine computed tomography (CT) scan during the staging and evaluation of disease. It is well known that a CT scan is an easy modality to estimate the skeletal muscle mass (SMM) in clinical practice, with cross-sectional image analysis at the level of the third lumbar vertebra (L3) as a standard landmark.[1]

The interactions between malnutrition, cachexia, and inflammation have been widely investigated but remain a matter of debate.[3] What seems clear is that a nutritional assessment, which should include an SMM evaluation, could be seen in a new light after the advent of immune checkpoint inhibitors (ICIs). Indeed, a recent study

reported that overweight sarcopenic melanoma patients experience more early acute limiting toxicity with anti-PD-1 checkpoint inhibitors.[4]

In a cohort of 81 advanced NSCLC patients treated with first-line chemotherapy, we recently found that baseline low SMI was also an independent predictor of shorter progression-free survival (PFS).[5] In that study, we performed subgroup analysis evaluating SMM at different time points.

Herein, we present a preliminary analysis performed on NSCLC patients in the above-mentioned cohort[5] with available CT scans at the start of second-line treatment with single agent nivolumab.

Methods

Study design

This is a retrospective observational analysis of stage IV NSCLC patients without common actionable biomarkers (*EGFR* mutations, *ALK* translocations, or PD-L1 ≥ 50% expression), treated with second-line nivolumab (3 mg/kg every two weeks) in clinical practice. The aim of this study was to evaluate the correlations between baseline SMM (categorized as low SMM and non-low SMM) and the following clinical outcomes: immune-related adverse events (irAEs) of any grade, G3/G4 irAEs, objective response rate (ORR), PFS, and overall survival (OS). ORR was defined as the portion of patients experiencing an objective response (complete response [CR] or partial response [PR]) as the best response to treatment. PFS was defined as the interval between treatment initiation and disease progression or death from any cause; OS as the interval between the beginning of treatment and death from any cause; and irAEs as AEs with an immunological basis. AEs were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0 and cumulatively reported as crude incidence. Responses were evaluated using Response Evaluation Criteria in Solid Tumors version 1.1.[6] Fisher's exact tests were used to correlate incidences of irAEs with baseline SMM. Median PFS and median OS were evaluated using the Kaplan–Meier method. The median follow-up period was calculated according to the reverse Kaplan–Meier method. Logrank tests were used to compare median PFS and median OS. The data cutoff period was August 2018. All statistical analyses were performed using MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018).

Patient eligibility and ethical aspects

Patients were eligible if they had a histologically confirmed diagnosis of measurable, stage IV NSCLC (both squamous and non-squamous) with available imaging assessment (CT or positron emission tomography-CT) performed before commencing treatment (no more than three months earlier). All patients provided written informed consent of the proposed treatment options. The procedures followed were in accordance with the precepts of Good Clinical Practice and the ethical standards of the local responsible committee on human experimentation (Comitato Etico per le province di L'Aquila e Teramo).

Anthropometric measurements and image analysis

Muscle mass was measured within CT images. Axial images of the abdomen were analyzed in a workstation using OSIRIX-Lite software V5.0 (Pixmeo, Sarl, Switzerland) by a single, trained observer blinded to patient outcomes. L3 with both transverse processes visible was chosen as the standard landmark. Skeletal muscle was quantified based on Hounsfield unit (HU) thresholds (-29 to $+150$) and SMM was evaluated using the skeletal muscle index (SMI, cm^2/m^2) for each patient. SMI was calculated by dividing the total cross-sectional skeletal muscle area (TMA - cm^2) at the level of lumbar vertebra L3 by squared height because TMA is linearly related to whole body muscle mass. TMA was computed for each patient with semi-automated specific tissue demarcation of the muscles in the L3 region (psoas, paraspinal, and abdominal wall muscles, excluding visceral organs). If other structures apart from those constituting TMA were automatically marked, they were eliminated by manual correction. To define low and non-low SMM we used gender-specific, body mass index (BMI)-incorporated, cutoff values of SMI (< 43 cm^2/m^2 for men with BMI < 25, <53 cm^2/m^2 for men with BMI ≥ 25, and < 41 cm^2/m^2 for women).[7]

Results

Patient features

From April 2015 to August 2018, 23 stage IV NSCLC patients treated with single agent nivolumab were eligible for image analysis. Nine (39.1%) patients had baseline low SMM. The patients' clinical features are summarized in Table 1. PD-L1 immunohistochemistry expression was only available in four patients – two were positive and two were negative – distributed equally among patient subgroups.
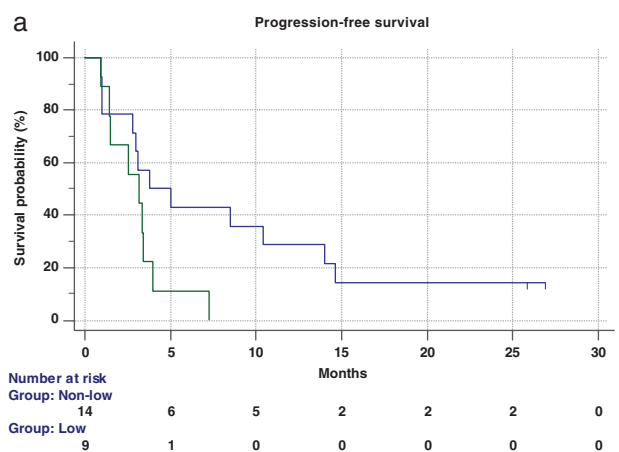
Clinical outcome analysis

ORR was 18.2% (95% confidence interval [CI] 4.9–46.5; 4 PR out of 22 evaluable patients). Among patients with low and non-low SMM, ORRs were 25% (95% CI 3.0–90.3;

Table 1 Patient features

Features	Number (%)
Patients	23 (100)
Gender	
Male	18 (78.2)
Female	5 (21.8)
Age	
Median (range)	67 (41–82)
Non elderly (< 70 years)	14 (60.9)
Elderly (≥ 70 years)	9 (39.1)
ECOG PS	
0	7 (30.4)
1	9 (39.2)
2	7 (30.4)
Histological subtype	
Squamous cell carcinoma	10 (43.5)
Non-squamous cell carcinoma	13 (56.5)
Sites of metastasis	
≤ 2	8 (34.8)
> 2	15 (65.2)
Weight (kg)	
Median (range)	76 (50–120)
BMI (kg/m^2)	
Median (range)	27.3 (19.1–45.2)
Underweight (BMI ≤ 18.5),	0
Normal weight (18.5 < BMI ≤ 24.9)	8 (34.8)
Overweight (25 < BMI ≤ 29.9)	8 (34.8)
Obese (BMI ≥ 30)	7 (30.4)
Lumbar skeletal muscle index (cm^2/m^2)	
Median	46.7
Range	(34.6–74.9)
Baseline low SMM	14 (60.9)

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; SMM, skeletal muscle mass.

2 PR out of 8 evaluable patients) and 14.3% (95% CI 1.7–51.6; 2 PR out of 14 evaluable patients), respectively, without significant difference ($P = 0.6019$).

At the median follow-up of 15.7 months, the median PFS and OS were 3.3 months (95% CI 2.8–5.0; 21 events) and 12.5 months (95% CI 4.1–14.6; 9 censored patients), respectively. In patients with low SMM, the median PFS and OS were 3.1 months (95% CI 1.4–3.4; 9 events) and 4.1 months (95% CI 1.5–6.6; 3 censored), respectively (Fig 1). In patients with non-low SMM, the median PFS and OS were 3.8 months (95% CI 2.8–14.0; 12 events) and 13 months (95% CI 4.7–14.5; 6 censored), respectively (Fig 1). Despite trends of longer median PFS and median OS in favor of patients with non-low SMM, no statistically significant differences were observed ($P = 0.0560$ and $P = 0.2866$, respectively).

Overall, 14 patients (60.9%) experienced irAEs of any grade: 3 (33.3%) patients with low SMM and 11 (78.6%) with non-low SMM ($P = 0.0771$). Overall, 2 patients (8.7%) experienced G3/G4 irAEs. None of the patients with low SMM experienced G3/G4 irAEs, while 2 (14.3%) patients with non-low SMM experienced G3/G4 irAEs.

Discussion

Despite the absence of statistical significance, the median PFS and OS appear decidedly longer among patients with non-low SMM compared to those with low SMM.

Looking to these findings, we must take into account the small sample size. Furthermore, to conduct an appropriate evaluation, we should have considered all other covariates, which surely affect clinical outcomes and body composition itself, such as age, performance status, histological subtype, and disease burden. On the other hand, the differences in survival rates between the subgroups seem to us so impressive that with a bigger sample size, statistically significant differences would emerge. Interestingly, our finding of a higher incidence of irAEs of any grade in
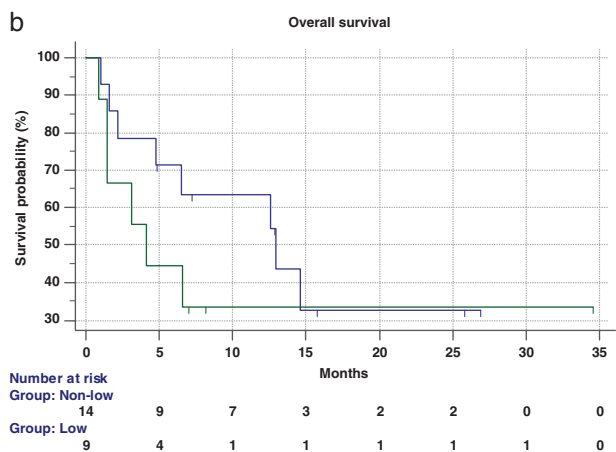

Figure 1 Kaplan–Meier survival analysis: log-rank test for (**a**) progression-free survival and (**b**) overall survival according to skeletal muscle mass (SMM) levels. SMM (———) non-low and (———) low.

patients with non-low SMM is consistent with recent reports that described significant associations between irAEs and a greater benefit with anti-PD-1/PD-L1 treatments.[8,9]

We cannot make any definitive conclusions, but only some speculative reflections on how nutritional status and body composition could affect the immune response and clinical outcomes of ICI treatments. Some authors have already speculated about the negative influence that alterations in body composition of sarcopenic patients could have on declining immunity.[10] A recent article further clarified that skeletal muscle cells actively modulate immune response in health and disease, particularly autoimmune diseases.[11] Indeed, they interact with immune cells like non-professional antigen presenting cells, expressing major histocompatibility complexes I and II and affecting T cell function.[11]

Moreover, skeletal muscle tissue could be an important IL-15 producer, which is necessary for natural killer (NK) cell function and homeostasis.[12] When muscle wasting is combined with elevated inflammatory cytokines (as occurs in cancer patients), we presume that it affects NK cell numbers and survival. In support of this possible role of IL-15, a recent preclinical study reported an increase in NK cell activation, with trans-presentation of IL-15 with an IL-15/IL-15Rα messenger RNA (the α portion of the IL-15 receptor) engineered human dendritic vaccine.[13] The role of NK cells in lung malignancies is still a matter of debate, but it is surely of clinical relevance,[14] particularly when looking at new treatment options, such as ICIs. Agents blocking the PD-1/PD-L1 pathway might enhance the cytotoxic action of activated NK cells, which express PD-1 in the tumor site.[15]

Very few studies have investigated the possible predictive role of sarcopenia for immunotherapy with ICIs. Some experiences have focused on safety, showing that sarcopenic melanoma patients are more likely to experience irAEs.[4,16] A large cohort study proposed a prognostic score, also based on SMM, which independently predicts survival, in patients with various malignances, treated with anti PD-1/PD-L1 agents.[17]

Surely, the vicious circle of chronic inflammation and malnutrition in cancer patients affects the immune response. From this point of view, the advent of ICIs could represent a revolution for therapeutic algorithms but also confirms the relevance of nutritional assessment of every patient at baseline.

The sample size of our study does not allow any consideration, but these preliminary results led us to plan a multicenter study of NSCLC patients treated with anti-PD-1 agents, with centralized evaluation of SMI in order to better define the possible impacts of sarcopenia on clinical outcomes with immunotherapy in NSCLC patients.

This hypothesis-generating preliminary report offers the opportunity to speculate on the influence of nutritional status and sarcopenia on immune response, suggesting these factors could affect treatment with nivolumab. Further studies are required and our next multicenter study will try to answer to some of the open questions on this topic.

Acknowledgment

Disclosure

No authors report any conflict of interest.

References

1 Bozzetti F. Forcing the vicious circle: Sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. *Ann Oncol* 2017; **28**: 2107–18.

2 Nakamura R, Inage Y, Tobita R et al. Sarcopenia in resected non-small cell lung cancer: Effect on postoperative outcomes. *J Thorac Oncol* 2018; **13**: 895–903.

3 Laviano A, Koverech A, Mari A. Cachexia: Clinical features when inflammation drives malnutrition. *Proc Nutr Soc* 2015; **74**: 348–54.

4 Heidelberger V, Goldwasser F, Kramkimel N et al. Sarcopenic overweight is associated with early acute limiting toxicity of anti-PD1 checkpoint inhibitors in melanoma patients. *Invest New Drugs* 2017; **35**: 436–41.

5 Cortellini A, Palumbo P, Porzio G et al. Single-institution study of correlations between skeletal muscle mass, its density, and clinical outcomes in non-small cell lung cancer patients treated with first-line chemotherapy. *Thorac Cancer* 2018; **9**: 1623–30.

6 Eisenhauer EA, Therasse P, Bogaerts J et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47.

7 Martin L, Birdsell L, Macdonald N et al. Cancer cachexia in the age of obesity: Skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 2013; **31**: 1539–47.

8 Toi Y, Sugawara S, Kawashima Y et al. Association of immune-related adverse events with clinical benefit in patients with advanced non-small-cell lung cancer treated with nivolumab. *Oncologist* 2018; **23**: 1358–65.

9 Riudavets M, Barba A, Maroto P et al. Correlation between immune-related adverse events (irAEs) and efficacy in patients with solid tumors treated with immune-checkpoints inhibitors (ICIs). *J Clin Oncol* 2018; **36** (15_Suppl): 3064.

10 Lutz CT, Quinn LS. Sarcopenia, obesity, and natural killer cell immune senescence in aging: Altered cytokine levels as a common mechanism. *Aging (Albany NY)* 2012; **4**: 535–46.

11 Afzali AM, Müntefering T, Wiendl H, Meuth SG, Ruck T. Skeletal muscle cells actively shape (auto)immune responses. *Autoimmun Rev* 2018; **17**: 518–29.

12 Quinn LS. Interleukin-15: A muscle-derived cytokine regulating fat-to-lean body composition. *J Anim Sci* 2008; **86**: E75–83.

13 Van den Bergh J, Willemen Y, Lion E *et al.* Transpresentation of interleukin-15 by IL-15/IL-15Rα mRNA-engineered human dendritic cells boosts antitumoral natural killer cell activity. *Oncotarget* 2015; **6**: 44123–33.

14 Carrega P, Ferlazzo G. Natural killers are made not born: How to exploit NK cells in lung malignancies. *Front Immunol* 2017; **8**: 277.

15 Pesce S, Greppi M, Tabellini G *et al.* Identification of a subset of human natural killer cells expressing high levels of programmed death 1: A phenotypic and functional characterization. *J Allergy Clin Immunol* 2016; **139**: 335–46.e3.

16 Daly LE, Power DG, O'Reilly Á *et al.* The impact of body composition parameters on ipilimumab toxicity and survival in patients with metastatic melanoma. *Br J Cancer* 2017; **116**: 310–7.

17 Dercle L, Ammari S, Champiat S *et al.* Rapid and objective CT scan prognostic scoring identifies metastatic patients with long-term clinical benefit on anti-PD-1/-L1 therapy. *Eur J Cancer* 2016; **65**: 33–42.