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LUNG CANCER (H BORGHAEI, SECTION EDITOR)

Poor-Performance Status Assessment of Patients with Non-small Cell Lung Cancer Remains Vague and Blurred in the Immunotherapy Era

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Abstract

Purpose of Review In the latest decade, the introduction of immune-checkpoint inhibitors (ICIs) has dramatically improved the prognosis of patients with NSCLC. First-line ICIs or chemo-ICI trials have demonstrated OS advantages but the accrual was limited to Eastern Cooperative Oncology Group (ECOG) performance status (PS)0-1 patients. ICI studies have for the vast majority excluded patients with poor performance status. PS 2 particularly is known as a negative prognostic factor for survival and a predictive factor of adverse events and poor response to treatments. Data on the activity of ICIs in PS2 patients are limited and come from heterogeneous meta-analyses and small phase II or expanded access trials. Often, terms such as "unfit" or "frail" ascertain the eligibility of patients to undergo cytotoxic chemotherapy, without specifying PS.

Recent Findings Other tools exist to aid in decision-making, and one simple, rapid, and validated screening test for frailty is the FRAIL scale consisting of 5 straightforward questions that can be self-administered and may represent an efficient and cost-effective way to screen large groups of patients for frailty. The Comprehensive Geriatric Assessment (CGA) is a widely used method to determine the medical, psychological, and functional capabilities of older patients. However, CGA is time-consuming and this could represent a real barrier to its adoption in clinical practice. For this reason, a quick screening tool, the G8 questionnaire, has been developed and demonstrated validity also in a younger population. A complementary tool to assess patients' frailty is Charlson comorbidity index (CCI) which has become the most widely used clinical index for a variety of disorders and cancers. Yet, none of these tools has been validated as predictive in ICI.

Summary In conclusion, solid data regarding the benefit of ICIs in ECOG PS2 NSCLC patients are currently lacking and the role of immunotherapy remains uncertain for PS2 patients. Prospective randomized trials addressing this question are warranted or ongoing. However, we are concerned that without a more extensive and objective assessment of patients' fitness and frailty by using and validating appropriate tools a clear answer may not come to light.

Keywords Performance status · Non-small cell lung cancer (NSCLC) · Frail · Unfit · Immunotherapy

Non-small cell lung cancer (NSCLC) remains one of the leading causes of cancer-related deaths, with a poor 5-year overall survival (OS) [1]. In the last decade, two major therapeutic developments have improved the prognosis of patients with NSCLC: targeted therapies in patients harbouring alteration-driven tumours, as well as the introduction of immune-checkpoint inhibitors (ICIs). First-line ICIs or chemo-ICI trials have demonstrated OS advantages but the accrual was limited to Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1 patients [2]. Unlike targeted therapy trials, which showed that the benefit extends to PS2 patients, ICI studies have for the vast majority excluded these patients [3, 4••]. In this viewpoint, we offer our interpretation of currently available data regarding the efficacy and tolerability of ICIs in PS2 patients, discussing alternative assessment options of patients' fitness and frailty.

All international treatment guidelines recommend first-line systemic therapy for advanced PS0–2 NSCLC patients [5, 6, 7•]. PS2 patients, representing those up and about over 50% of the time, but unable to conduct a physically strenuous activity,

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account for approximately 35% of NSCLC patients [8, 9]. PS2 is a known negative prognostic factor for survival and a predictive factor of adverse events and poor disease response to treatments [10]. However, in this patient group, single-agent chemotherapy prolongs survival and improves quality of life (QoL) as compared with best supportive care (BSC) and some chemotherapy doublets showed tolerable toxicity profiles and favourable outcomes, suggesting that these patients should not be under-treated [11].

As recently summarized by Passaro et al [12], there have been 11 phase III studies to assess the efficacy of ICIs in locally advanced or metastatic NSCLC studies but only a small number of patients were PS2. Data on the activity of ICIs in PS2 patients are scant and come from heterogeneous meta-analyses and small phase II or expanded access trials.

To further complicate matters, knowing that the PS2 patient population is heterogeneous, it is important to understand how reliable and reproducible the PS assessment is. Defining fitness only according to PS is indeed influenced by the assessor's subjectivity and by discrepancies between the commonly used ECOG PS and Karnofsky Index scores. Several factors can lead to PS deterioration: the burden of the disease itself, the presence of comorbidities and the global frailty of elderly people; nevertheless, poor PS is not evaluated as a diverse entity according to its cause.

Often, terms such as "unfit" or "frail" ascertain the eligibility of patients to undergo cytotoxic chemotherapy, without specifying PS. For the National Comprehensive Cancer Network (NCCN), "unfit" represents an ECOG PS of 3–4. "Frailty" is a state of diminished physiologic reserves that results in increased vulnerability to stressors (cancer, treatments) and a higher risk of adverse events (complications, dependency, death) [13]. Based on the recommendation of a frailty consensus group consisting of delegates from 6 major international, European and US societies, all people older than 70 years and all individuals with significant weight loss (> 5%) due to chronic disease should be screened for frailty [14]. Although it is well recognized that frailty is not related only to older age, the adequate identification of "frail" patients can be challenging since no international standardization of frailty cut-offs have been validated or widely accepted. However, several general frailty scales are available and could adequately measure different aspects that relate to this condition, such as mobility, function, energy, nutrition, comorbidities, social vulnerability, mood and cognition [13]. One simple, rapid and validated screening test for frailty is the FRAIL scale consisting of 5 straightforward questions that can be self-administered and may represent an efficient and cost-effective way to screen large groups of patients for frailty (see Fig. 1) [15].

There are also validated tools that could be utilized to better evaluate elderly patient frailty. For instance, the Comprehensive Geriatric Assessment (CGA) is a widely used method to determine the medical, psychological and functional capabilities of older patients and different components of the CGA can be useful to predict treatment toxicity and functional decline [16•]. However, a complete CGA is time consuming and this could represent a real barrier to its adoption in clinical practice. For this reason, a quick and easy-to-use screening tool, the G8 questionnaire, has been developed and has also demonstrated its validity in a younger population [17]. It consists of 7 items including a mini-nutritional assessment (see Fig. 1). The G8 questionnaire is a convenient screening tool for geriatric assessments since a complete CGA should follow in patients with a score ≥ 14, but it has also demonstrated the ability to detect functional decline and predict survival in the elderly and lung cancer patients [18–21].

A possible complementary tool to assess patients' frailty is the Charlson comorbidity index (CCI) [22••]. The CCI score was first developed in 1984 by reviewing hospital charts to assess 1-year mortality and was validated in a cohort of 685 breast cancer patients. Each among 19 medical conditions was assigned a weight, and the index was the summation of all scores [23]. Since then, the CCI score has become the most widely used clinical index for a variety of disorders and cancers. The suggested cut-off for patients with lung cancer is of 9 [24]. Because age has been determined to influence survival, the CCI was amended with a correction by age by Charlson et al in 1994, resulting in the age-adjusted Charlson comorbidity index (ACCI) [25]. The ACCI is a prognostic classification developed for patients with comorbid conditions. As PS does not necessarily translate into a greater number of comorbidities, the ACCI can have significant discrepancies with PS. In a recent retrospective, single centre study of 75 elderly patients receiving ICI for advanced NSCLC, PS was shown to be the greatest predictor of survival, with a highly significant difference in OS between PS0–1 and ≥ 2 (13.7 versus 3.8-month OS). In this series, ACCI was not an independent predictive factor for survival or treatment failure [26].

Even if conflicting data exist about the adequate evaluation of unfit or frail patients and none of the several currently available tools has been yet properly assessed and further validated in prospective lung cancer treatment trials, we believe that these tools could be clinically useful to address the clinical heterogeneity that exists among ECOG poor PS NSCLC patients (see Fig. 2).

In the latest ESMO guidelines [27], the level IA recommendation for first-line pembrolizumab has been limited to ECOG PS0–1 patients. For PS2 patients, carboplatin-based or single-agent chemotherapy are recommended, independently of PD-L1 expression. ICIs are an option, with a level IIIB recommendation, due to lack of data. In the second-line, three ICIs are recommended with level IA for PS0–2 patients. In this case, the favourable toxicity profile of ICI led to their extension to PS2 patients in spite of a lack of evidence due to study design and patient selection in registration trials, aimed at optimizing outcomes.

The FRAIL Scale[a]		
Acronym	Task	Question
F	Fatigue	Do you feel tired most or all the time?
R	Resistance	Can you climb 1 flight of stairs without difficulty?
A	Ambulation	Can you walk 1 block without assistance?
I	Illness	Do you have greater than 5 illnesses?
L	Loss of weight	Have you lost >5% of your usual weight in the last year?
[a]Scoring: 0 indicates robust; 1-2, prefrail; ≥ 3, frail		

G8 questionnaire

	Items	Possible answers (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 : severe decrease in food intake
		1 : moderate decrease in food intake
		2 : no decrease in food intake
B	Weight loss during the last 3 months	0 : weight loss > 3 kg
		1 : does not know
		2 : weight loss between 1 and 3 kgs
		3 : no weight loss
C	Mobility	0 : bed or chair bound
		1 : able to get out of bed/chair but does not go out
		2 : goes out
E	Neuropsychological problems	0 : severe dementia or depression
		1 : mild dementia or depression
		2 : no psychological problems
F	Body Mass Index (BMI (weight in kg) / (height in m²)	0 : BMI < 19
		1 : BMI = 19 to BMI < 21
		2 : BMI = 21 to BMI < 23
		3 : BMI = 23 and > 23
H	Takes more than 3 medications per day	0 : yes
		1 : no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0 : not as good
		0.5 : does not know
		1 : as good
		2 : better
	Age	0 : >85
		1 : 80-85
		2 : <80
	TOTAL SCORE	0 – 17

The age-adjusted Charlson Comorbidity Index

Score	Comorbid condition
1	Myocardial infarction (MI)
	Congestive heart failure (CHF)
	Cerebral vascular disease
	Peripheral vascular disease
	Dementia
	Chronic obstructive pulmonary disease (COPD)
	Connective tissue disease
	Peptic ulcer disease (PUD)
	Mild liver disease
	Age[a]
2	Diabetes
	Hemiplegia
	Moderate/severe renal disease
	Diabetes with end-organ damage
	Any solid tumor
	Leukemia
	Lymphoma
3	Moderate/severe liver disease
6	Metastatic solid tumor
	Acquired immunodeficiency syndrome (AIDS)

[a] For each decade after 40 years, a point is added (1 point for age group 41–50, 2 points for age group 51–60, 3 points for 61–70, 4 points for 71 or older).

Fig. 1 FRAIL scale, G8 questionnaire and age-adjusted Charlson Comorbidity Index

Despite the limited data available, several oncology societies, including the NCCN, have extended recommendations for first-line ICI to PS2 patients, leaving the responsibility to physicians' discretion.

In our daily practice, we evaluate each PS2 NSCLC patient individually when considering ICIs. In spite of the current lack of evidence, we do treat some PS2 patients with immunotherapy. At the moment, we do not routinely use any of the additional assessment tools, as they have not been validated in this setting. We more readily administer ICI when the loss of performance stems from cancer, rather than irreversible comorbid diseases. Furthermore, a less aggressive tumour presenting with a progressive performance decline would also tilt the balance in favour of ICI among these patients, as we suspect the benefit of therapy and its impact on prognosis could be more meaningful in these cases.

In conclusion, solid data regarding the benefit of ICIs in ECOG PS2 NSCLC patients are currently lacking and the role of immunotherapy remains uncertain for PS2 patients. Prospective randomized trials addressing this question are warranted or ongoing. However, we are concerned that without a more extensive and objective assessment of patients' fitness and frailty by using and validating appropriate tools, a clear answer may not come to light anyway.

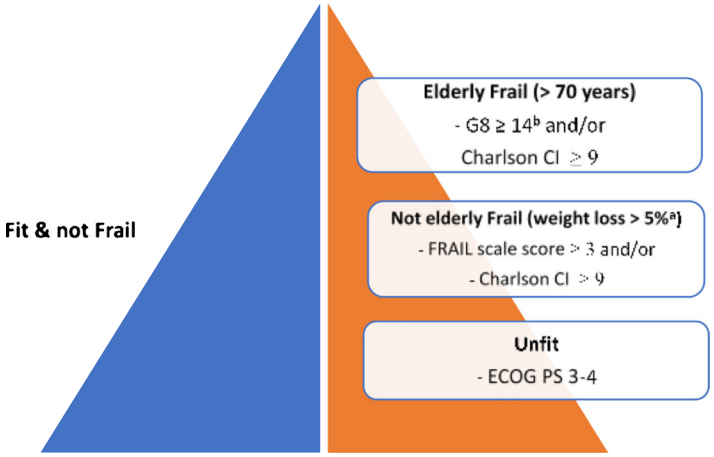

Fig. 2 Proposed fitness and frailty assessment for patients with NSCLC

[a]Due to chronic disease
[b]A Comprehensive Geriatric Assessment is needed
Abbreviations: CI, comorbidity index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non small cell lung cancer.

Compliance with Ethical Standards

Conflict of Interest Alex Friedlaender has received compensation from Roche, Pfizer, Astellas and Bristol-Myers Squibb for service as a consultant.

Giuseppe Luigi Banna has received compensation from Merck Sharpe & Dohme, Boehringer Ingelheim, Janssen-Cilag and Roche for participating on advisory boards.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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