Editorial

Is there really a role for the comprehensive geriatric assessment in metastatic non-small cell lung cancer?

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Comment on: Corre R, Greillier L, Le Caër H, *et al.* Use of a Comprehensive Geriatric Assessment for the Management of Elderly Patients With Advanced Non-Small-Cell Lung Cancer: The Phase III Randomized ESOGIA-GFPC-GECP 08-02 Study. J Clin Oncol 2016;34:1476-83.

Submitted Feb 18, 2016. Accepted for publication Feb 26, 2016.
doi: 10.21037/tcr.2016.04.11
View this article at: http://dx.doi.org/10.21037/tcr.2016.04.11

Lung cancer is the most common cancer worldwide and the leading cause of cancer-related deaths (1,2). About 50% of patients with non-small cell lung cancer (NSCLC) are older than 65 year-old, and median ages at diagnosis are currently 63–70 in Western countries (3). Due to demographic trends and CT-based screening, incidence of NSCLC in elderly is expected to increase. Therefore, the management of these patients is a challenge for the medical community.

Difficulties in management of elderly might be explained by different problems. On the one hand, despite increasing evidence of chemotherapy benefit (4), elderly are often undertreated, because of the nihilism of both doctors, families and patients. On the second hand, elderly are more prone to toxicities and treatment-related mortality, and overtreatment needs to be prevented. Finally, they are too often excluded from clinical trials (5) and there are very few studies dedicated to this population, which makes guidelines difficult to establish. For all these reasons, it is crucial to optimize treatment in elderly patients to better assess the risk-benefice ratio, identifying those who are likely to benefit from chemotherapy of those who are likely to have too much toxicity.

The first trial demonstrating the benefit of single-agent chemotherapy in elderly patients was the Elderly Lung Cancer Italian Study (ELVIS) (6). After that, international guidelines have recommended single-agent therapy as the treatment of choice for elderly population (7,8). Some sub-groups or retrospective analyses from randomized trials then suggested that a platinium-based doublet was feasible and efficient in fit elderly patients (9,10). The current evidence-based for a carboplatin-based doublet as a standard of care in elderly patients was demonstrated by the Intergroupe Francophone de Cancérologie Thoracique (IFCT)-0501 phase III trial. Monthly carboplatin and weekly paclitaxel doublet chemotherapy regimen have been compared with single-agent regimen (either vinorelbine or gemcitabine) in 451 elderly patients with a PS of 0 to 2 with advanced NSCLC (11). Despite increased but manageable toxic effects, doublet chemotherapy was associated with survival benefits compared to monotherapy, with a median overall survival (OS) of 10.3 *vs.* 6.2 months respectively (HR, 0.64; 95% CI, 0.52–0.78; P<0.0001). Two other phase III studies have confirmed these findings (12,13). Therefore, today's guidelines recommend carboplatin-based doublet as first-line treatment for fit elderly NSCLC patients, whereas single-agent treatment (gemcitabine, vinorelbine, taxanes) represents a valid option for less fit patients (14).

But what is a fit patient? How can we precisely define a fit patient? Age and Performance Status (PS) are not sufficient to assess the capacity of an elderly to receive CT: comorbidities, age-related physiological variations of the main body functions, long-term treatments, polypharmacy, and social setting must also be considered for the therapeutic algorithm. Basic and reproducible geriatric assessment tools have to be developed in this way. Comprehensive Geriatric Assessment (CGA) is a multidisciplinary and global scale evaluating comorbidities, functional status, cognition, emotional status, social and environmental situation, nutritional status, mental health, polypharmacy, and geriatric syndromes. Its objectives are multiple: detecting unknown health problems, evaluating patients vulnerability, preventing iatrogenic effects and functional decline, managing pain and offering psychological support to elderly patients. It aims to reduce

both undertreatment as well as overtreatment. CGA have been shown to predict morbidity and mortality in elderly patient treated for cancer (15) and to prevent treatment toxicity in solid cancers (16). Balducci and Extermann used a CGA-based approach to stratify patients in three groups (fit, vulnerable and frail patients) with three adapted treatment options [standard therapy, adjusted therapy, and best supportive care (BSC) respectively] (17).

Until now, even if the use of CGA is encouraged in guidelines, this is mainly on the bases of retrospective studies and no instrument has been shown to improve treatment selection when added to the routine geriatric oncology patient evaluation.

Corre *et al.* have tried to answer to the question in the Elderly Selection on Geriatric Index Assessment (ESOGIA)-Groupe Français de Pneumo-Cancérologie (GFPC)—Grupo Español de Cáncer de Pulmón (GEPC) 08-02 study (18). This is the first phase III randomized trial comparing in first line a standard strategy of treatment allocation (carboplatin-based doublet or single agent on the basis of PS and age) with experimental CGA-based allocation of the same chemotherapies or BSC. The choice of the chemotherapy regimen is somewhat strange because it adds some complexity to the analysis and is not part of the usual ones, but study was designed before the IFCT-0501 trial and the corresponding recommendations about carboplatin plus weekly-paclitaxel regimen.

The primary endpoint was treatment failure-free survival (TFFS), defined as the time of elapsing between randomization and treatment discontinuation resulting of any reason (disease progression, treatment toxicity, and death). This combined primary endpoint was particularly adapted to elderly patients, taking into account not only progression but also tolerability and death from other causes than cancer. CGA-based treatment allocation failed to improve the TFFS or OS: median TFFS was 3.1 months (2.7–4.4 months) for CGA arm versus 3.2 months (2.9–4.1 months) for standard arm (P=0.32); median OS was 6.1 versus 6.4 months respectively (P=0.87). Nevertheless, patients in CGA arm seemed to be better oriented and to receive a more appropriate treatment: more patients received doublet chemotherapy (45.7% *vs.* 35.1% in the standard group), and 23% were assigned to BSC. As a result, patients in the CGA arm experienced significantly less all grade toxicity (85.6% *vs.* 93.4% respectively, P=0.015) and less toxicity-related treatment failure (4.8% *vs.* 11.8%, P=0.007). Furthermore, CGA identified patients with a poor natural prognosis: median OS BSC was only 2.8 months, which is significantly lower than in other studies (11).

Several geriatric indexes have been shown as independent prognostic factors in lung cancer, such as ADL in the IFCT-0501 study (11), IADL (19) or BMI (20). But the main problem is that none of these factors has ever demonstrated any predictive value. So how relevant the use of CGA is in lung cancer? This tool is time consuming and hard to apply in routine care (approximately one supplementary hour per patient, which will require more medical time or more physicians). Should it be of no help to predict outcomes, maybe it does not make sense to use it for each patient. The cutoffs used to define fit, vulnerable, and frail patients may not be the most appropriate in advanced NSCLC, probably because most of patients die of cancer rather than comorbidities (11,18).

The authors conclude saying that the use of CGA in this setting cannot be routinely advised in clinical practice. Waiting for this, simplified geriatric assessment adding to PS, such as body mass index, Charlson comorbidity index, or ADL would be of interest and their predictive value have to be studied.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Shao-Hua Cui (Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.04.11). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Leduc C, Quoix E. Is there really a role for the comprehensive geriatric assessment in metastatic non-small cell lung cancer? Transl Cancer Res 2016;5(S1):S44-S46. doi: 10.21037/tcr.2016.04.11

