Commentary

Treatment dilemma in the care of older adults with advanced lung cancer

Ajeet Gajra[1], Ankit Anand[1], Kah Poh Loh[2], Supriya Mohile[2]

[1]Hematology-Oncology, Upstate Cancer Center, SUNY Upstate Medical University, Syracuse, NY13210, USA; [2]Hematology Oncology, James P Wilmot Cancer Institute, University of Rochester, Rochester, NY 14642, USA

Correspondence to: Ajeet Gajra, MD, FACP, Associate Professor of Medicine. SUNY Upstate Medical University, Syracuse, NY 13210, USA. Email: gajraa@upstate.edu.

Submitted Sep 29, 2016. Accepted for publication Oct 12, 2016.
doi: 10.21037/jtd.2016.11.73
View this article at: http://dx.doi.org/10.21037/jtd.2016.11.73

There are persistent knowledge gaps in the management of older patients with advanced lung cancer. Despite significant advances in the treatment over the past decade, mortality from lung cancer continues to increase in patients over age 70 years (1). Thus, advances in the treatment of lung cancer have minimally impacted this large subgroup of population. While patients 70 years or older account for almost half the patients with lung cancer, they are typically under-represented on clinical trials (1). In the NCI cooperative group trials, while close to 40% of patients are aged 75 and over, only 15% of patients in this age range are on clinical trials (2). Further, the majority of age-unspecified clinical trials include only the fittest of elderly patients due to their stringent eligibility criteria (3). Given the high prevalence of multimorbidity, impairment in physical function and limited social support amongst elderly, the management of this patient group has not been studied in a systematic manner. The issue of single-agent versus combination platinum-based chemotherapy also remains in question for the elderly. The recent IFCT-0501 (Intergroupe Francophone de Cancérologie Thoracique) trial did confirm the superiority of carboplatin and paclitaxel based doublet chemotherapy in elderly patients with good performance status (PS) when compared to single agent gemcitabine or vinorelbine (4). However, this trial too included essentially fit patients as it excluded "patients with co-morbidities that impaired administration of chemotherapy or who had respiratory impairment that required chronic oxygen". Even within this group of healthier elderly, there was increased toxicity in the combination chemotherapy arm; chemotherapy -associated mortality was 4.4% in doublet arm compared to only 1.3% in single agent arm. There was more hematologic and non-hematologic toxicity in the combination arm; the rates of grade 3 and grade 4 neutropenia were 48.4% *vs.* 12.4%, febrile neutropenia was 9.4% *vs.* 2.7%, thrombocytopenia was 6.7% *vs.* 0.9% in the doublet and single arms respectively. As a consequence, thoracic medical oncologists continue to face the dilemma of over-treatment versus under-treatment in the management of older adults with advanced lung cancer. It is important to risk stratify older adults; good risk patients may be treated with a platinum-based doublet chemotherapy since failure to do so can lead to compromised efficacy. However, vulnerable patients may suffer excessive toxicity and discontinuation of chemotherapy as a consequence, thereby limiting outcomes. There is a great need to balance efficacy of chemotherapy with adverse events in older adults who are prone to all chemotherapy associated toxicity.

Comprehensive geriatric assessment (CGA) refers to a multidisciplinary comprehensive evaluation of an individual's functional status, comorbid conditions, cognition, psychology, social support system, nutritional status and review of the patient's medications. Geriatric assessment can be valuable in risk stratifying older patients. Nevertheless, a CGA is rarely performed, even in trials limited to older adults with cancer. A number of trials have assessed the association of some components of geriatric assessment with outcome. For example, the MILES trial which studied its association of activities of daily living (ADLs), instrumental activities of daily living (IADLs) and quality of life with outcomes in patients over age 70 years with stage 3B and stage 4 lung cancer (patients were

randomized to gemcitabine, vinorelbine or the combination of the two agents) (5). This study enrolled patients with ECOG PS ≤2 and out of 707 patients initially randomized, 141 (20.1%) patients were removed from analysis due to lack of information on IADLs and quality of life (QOL) measures. After adjusting in multivariate analysis; QOL, IADLs (not ADLs), ECOG PS 2 were associated with prognosis (6). Interestingly, Charlson score was not associated with prognosis. A possible explanation for this lack of association may be that patients with higher Charlson score were not enrolled on the study due to the exclusion criteria specified in the study. The Charlson score was categorized into 4 groups for analysis (0, 1, 2 and ≥3) with only 11% patients reporting no significant comorbid condition. Further, it is possible that to be able to have an effect on survival, a patient's life expectancy from comorbidities should be longer than that from advanced lung cancer (3). Caillet *et al*. reviewed multiple studies (19 of the 29 studies included patients with lung cancer) in a systematic manner and concluded that CGA in elderly patients can affect treatment decisions in up to 21–49% of patients. After adjusting in multivariate analysis, there was significant association of CGA domains including functional impairment, malnutrition and comorbidities with overall survival (OS) and treatment related toxicity (7). It is a common practice in oncology to make treatment recommendations based on performance status (PS), however PS does not take in to account comprehensive evaluation of various age-related factors and CGA adds valuable information on functional assessment of elderly patients (8). In a prospective study of 200 elderly cancer patients (>70 years), CGA was more sensitive in detecting patients who were unfit for chemotherapy (9). While medical oncologists continue to rely on PS for decision making, it is not consistently captured and there is limited data regarding the concordance of PS assessment by the physician and as self-evaluated by the patient. In at least one study in lung cancer, there was a lack of documentation of PS in up to 20% of patient charts (10). Approximately 20% of older patients with cancer present with ECOG PS of at least 2 and more than 50% of these patients need assistance with IADLs (10,11). In the NVALT phase 3 study, CGA was performed in patients older than 70 years undergoing chemotherapy for advanced NSCLC. Study population had a median Charlson Comorbidity index of 1 and 23% required assistance with ADLs, 53% required assistance with IADLs, 7% were cognitively impaired and 27% were depressed. To reduce the problem of multiplicity, authors undertook a primary component analysis and they identified only one dominant dimension which was significantly prognostic. Groningen frailty indicator and geriatric depression scale were its largest contributors (12).

In light of the above, it is especially relevant that Corre and colleagues recently reported on the first of its kind, phase III randomized controlled trial that utilized CGA in decision making for treatment allocation in older patients with advanced NSCLC (13). It is noteworthy that it has taken more than 10 years of research in geriatric oncology to come up with the first phase III randomized controlled trial that incorporates CGA for treatment allocation and we applaud the authors for this achievement. Corre *et al*. used the approach devised by Balducci and Extermann to define three therapeutic groups of elderly patients: standard therapy for fit patients, palliative care for frail patients and adjusted therapy for vulnerable patients (14).

In this novel clinical trial, patients age 70 years or older with ECOG performance status of 0-2 were randomized to one of two arms: standard arm comprised of chemotherapy allocation based on PS and age which mandated a carboplatin-based doublet for PS 0 and age 75 or less, but single agent docetaxel if PS was 2 and/or age older than 75 years. The experimental arm utilized CGA based chemotherapy allocation: fit patients received carboplatin-based doublet, vulnerable patients were treated with single agent docetaxel and frail patients received best supportive care (BSC) only. The primary end point was treatment failure-free survival (TFFS) with secondary end points of OS, progression-free survival, tolerability, and quality of life. Almost 500 patients were enrolled with a median age of 77 years (standard arm, n=251; CGA arm, n=243). It is noteworthy that on the CGA arm, 23% patients received BSC only. A greater proportion of patients received doublet chemotherapy in the CGA guided arm (45.7% and 35.1%) and almost twice as many patients received monotherapy on the standard arm (64.9% *vs*. 31.3%). The primary endpoint of median TFFS times was not improved by 30% in the CGA arm which was the statistical premise [3.2 and 3.1 months, respectively for standard and CGA arm, hazard ratio (HR) =0.91; 95% CI: 0.76–1.1] and hence, this trial is deemed by some as a "negative" trial. Similarly, the median OS times were 6.4 and 6.1 months, respectively (HR =0.92; 95% CI: 0.79–1.1). However, patients in the CGA arm, compared with standard arm patients, experienced significantly less all grade toxicity (85.6% *vs*. 93.4%, respectively; P=0.015) and fewer treatment failures as a result of toxicity (4.8% *vs*. 11.8%, respectively; P=0.007).

Since advanced lung cancer is an aggressive malignancy and most patients die because of progressive cancer, TFFS may not be the best endpoint, which is preferable for more indolent tumors. As stated above, greater proportion of patients received doublet chemotherapy in the CGA arm. While the statistical significance is not reported, patients on CGA directed doublet therapy had the best numeric values for median TTFS, PFS and OS of all patients groups included. It is obvious that the survival end-points were lower in this intent-to-treat analysis as a consequence of the patients with BSC in the CGA arm. While exploratory, it would be interesting to assess the efficacy endpoints after excluding patients with BSC. A significant criticism of the study design would be that the patients in the standard therapy arm were risk-stratified to a great extent (as based on age and PS). This type of allotment (especially the age cut-off) is not considered standard. Further, patients with PS2 have been shown to benefit from doublet chemotherapy as well (15). Thus, there is no real basis for this assignment within the standard arm. Another important consideration on the CGA arm pertains to the definition of vulnerable and frail patients based on CGA. In this study, presence of only one geriatric syndrome such as urinary or fecal incontinence or geriatric depression scale score of 4–5 was considered frail, despite being independent with all ADLs and IADLs. There is also a lack of nutritional status assessment in CGA. There needs to be some refinement of these definitions for use in future studies. Alternatively, a risk-based stratification may be appropriate using validated scores such as the CARG (Cancer and Aging research group) and CRASH toxicity tools (16,17). Patients may then be assigned to varying chemotherapy intensity based on pre-therapy risk assessment scores.

Another clinically meaningful finding from the ESOGIA study is the identification of factors associated with poor TTFS in a multivariate analysis of the study population. These include: body mass index ≤ 20 kg/m^2, former or current smoking status, <4 chemotherapy cycles, Charlson comorbidity index ≥ 2, and the existence of a geriatric syndrome. These can serve as stratification factors for future trials in this population. Further, in this trial population, 76.1% patients had Charlson comorbidity index of 0 or 1, 14.3% required assistance with ADLs, 29.6% required assistance with IADLs, 15.4% were cognitively impaired, 9.3% had geriatric syndromes and 16.6% were depressed (2). Outside the clinical trial setting in patients with NSCLC, mean Charlson comorbidity index 3 (range, 0–9) and 17% had Charlson comorbidity index of 0 or 1. CGA detected 48.2% patients who required assistance with ADLs, 69.9% required assistance with IADLs dependency, 26.4% were cognitively impaired, 55.4% had weight loss (mean % weight loss was 8.2%) and 48.2% had geriatric syndrome (18). This ESOGIA as well as the NVALT 3 studies essentially included a healthier clinical trial population as opposed to that seen in general practice.

Despite its limitations, overall, the ESOGIA trial represents a major step in the evolution of geriatric oncology research. While modifications are needed for future trial design, it has established a broad principle that it is feasible to incorporate CGA in a multicenter clinical trial setting; and that CGA based therapy was associated with decreased toxicity in this patient population. A possible design for older patients with advanced NSCLC especially in US (where BSC mandate will likely not be well-received by patient groups and institutional review boards) may include: standard arm- where chemotherapy doublet or single agent is at the discretion of the treating oncologist. CGA based arm: wherein treatment is assigned based on the CGA derived validated toxicity predictive model. E.g., single agent for patients at high risk for chemotherapy toxicity and doublet for those at low- medium risk. In an ideal trial design CGA data would be collected on all patients (even those in the standard arm) but the treatment team can be kept blinded in the standard arm. Two possible methods to circumvent the "contamination or accidental unblinding" on the standard arm would be: (I) randomize centers (rather than patients) to either standard or CGA arms to limit exposure of the treating oncologists to findings of the CGA and their significance; (II) consider a registration process wherein the patient and the oncologist fill in the CGA questionnaire (preferably online) which is then mailed in (electronically captured) to central registration and the treatment allocation.

In conclusion, the role of CGA in treatment assignment and risk stratification of elderly patients with advanced NSCLC has not ended with ESOGIA trial; rather, this trial marks the beginning of an era of greater inclusion of CGA in the management of elderly patients with cancer.

Acknowledgements

None.

Footnote

Provenance: This is an invited Commentary commissioned by the Section Editor Long Jiang (Second Affiliated Hospital, Institute of Respiratory Diseases, Zhejiang

University School of Medicine, Hangzhou, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

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.

References

1. Owonikoko TK, Ragin CC, Belani CP, et al. Lung cancer in elderly patients: an analysis of the surveillance, epidemiology, and end results database. J Clin Oncol 2007;25:5570-7.
2. Mooney MM. Older Patients in NCI-sponsored Clinical Treatment Trials. Available online: http://meetinglibrary.asco.org/content/68859?media=vm
3. Shenoy P, Harugeri A. Elderly patients' participation in clinical trials. Perspect Clin Res 2015;6:184-9.
4. Quoix E, Zalcman G, Oster JP, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 2011;378:1079-88.
5. Gridelli C, Perrone F, Gallo C, et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst 2003;95:362-72.
6. Maione P, Perrone F, Gallo C, et al. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol 2005;23:6865-72.
7. Caillet P, Laurent M, Bastuji-Garin S, et al. Optimal management of elderly cancer patients: usefulness of the Comprehensive Geriatric Assessment. Clin Interv Aging 2014;9:1645-60.
8. Repetto L, Fratino L, Audisio RA, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol 2002;20:494-502.
9. Wedding U, Ködding D, Pientka L, et al. Physicians' judgement and comprehensive geriatric assessment (CGA) select different patients as fit for chemotherapy. Crit Rev Oncol Hematol 2007;64:1-9.
10. Salloum RG, Smith TJ, Jensen GA, et al. Using claims-based measures to predict performance status score in patients with lung cancer. Cancer 2011;117:1038-48.
11. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 2007;25:1824-31.
12. Biesma B, Wymenga AN, Vincent A, et al. Quality of life, geriatric assessment and survival in elderly patients with non-small-cell lung cancer treated with carboplatin-gemcitabine or carboplatin-paclitaxel: NVALT-3 a phase III study. Ann Oncol 2011;22:1520-7.
13. 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.
14. Balducci L, Extermann M. Management of cancer in the older person: a practical approach. Oncologist 2000;5:224-37.
15. Zukin M, Barrios CH, Pereira JR, et al. Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. J Clin Oncol 2013;31:2849-53.
16. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 2011;29:3457-65.
17. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer 2012;118:3377-86.
18. Gironés R, Torregrosa D, Maestu I, Gómez-Codina J, Tenias JM, Costa RR. Comprehensive Geriatric Assessment (CGA) of elderly lung cancer patients: a single-center experience. J Geriatr Oncol 2012;3:98-103.

Cite this article as: Gajra A, Anand A, Loh KP, Mohile S. Treatment dilemma in the care of older adults with advanced lung cancer. J Thorac Dis 2016;8(11):E1497-E1500. doi: 10.21037/jtd.2016.11.73

