Editorial

Treatment of limited-stage small cell lung cancer in the elderly, chemotherapy *vs.* sequential chemoradiotherapy *vs.* concurrent chemoradiotherapy: that's the question

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Abstract: Chemotherapy is the mainstay of the treatment in limited disease (LD) and extended disease (ED) small cell lung cancer (SCLC) patients, while concurrent chemoradiotherapy (CRT) is the standard of care in healthy patients with LD. However, this intensive treatment is associated with significantly more toxicity in the subset of patients aged 70 years or more. To date, most of available data concerning CRT in elderly derived from retrospective analyzes, usually conducted on small samples of patients, poorly representative of this population. Modern CRT appears to confer a survival benefit compared to chemotherapy alone in a recent retrospective analysis conducted on elderly patients with LD-SCLC. Age alone should not be a contraindication for multimodality treatment in this subset of patients.

Keywords: Chemoradiotherapy (CRT); elderly; limited disease (LD); thoracic radiotherapy; small cell lung cancer (SCLC)

Submitted Jan 30, 2016. Accepted for publication Feb 01, 2016.
doi: 10.21037/tlcr.2016.03.03
View this article at: http://dx.doi.org/10.21037/tlcr.2016.03.03

Small cell lung cancer (SCLC) is an aggressive pulmonary tumor characterized by a rapid doubling time, high growth fraction, and the early development of widespread metastases. It represents approximately 15% of new lung cancer diagnosis each year and its incidence increases with age, about 45% of these involved patients older than age 70 years (1). According to the Veteran's Administration Lung Study Group's 2-stages classification scheme, the extension of disease in patients with SCLC is distinguished in: limited disease (LD)-SCLC, defined as a tumor that is confined to ipsilateral hemithorax, mediastinal, or supraclavicular lymph nodes, which can be safely encompassed within a radiation field (about one-third of cases), and extensive disease (ED), where the tumor is not confined to one hemithorax or has malignant pleural or pericardial effusion or hematogenous metastases (2). Chemotherapy (CT) is the mainstay of the treatment in LD- and ED-SCLC patients, while concurrent chemoradiotherapy (CRT) is the standard of care in healthy patients with LD. In 1992, two meta-analyses were published regarding the role of thoracic radiotherapy in addition to CT in LD-SCLC (3,4). The first meta-analysis, including 2,140 patients with LD-SCLC from 13 trials (433 patients with ED-SCLC were excluded), evaluated the hypothesis that thoracic radiotherapy contributes to a moderate increase in overall survival (OS) (3). The relative risk of death in the combined-therapy group as compared with the CT group was 0.86 [95% confidence interval (CI), 0.78–0.94; P<0.001], corresponding to a reduction of 14% in the mortality rate. The benefit in term of 3-year survival rate was 5.4%±1.4%, although it wasn't evident in patients older than age 70 years: the relative risk of death in the combined-therapy group as compared with the CT group ranged from 0.72 in patients younger than 55 years (95% CI, 0.56–0.93) to 1.07 for those over 70. This result was probably, but not confirmed, related to increased toxicity in the older patients (3). The second meta-analysis reported a small but significant improvement in survival and a major improvement in local (intrathoracic) tumor

control in patients receiving CRT treatment, although it was associated with a small increase in treatment-related mortality (4).

Unlike, retrospective analyses do not justify a different approach between the elderly and young patients (5-8). First, there is a retrospective review of data from 608 patients aged 80 years or less with LD-SCLC, who participated in two previously reported randomized trials (BR.3 and BR.6) of the National Cancer Institute of Canada: all patients received the same CT, consisting of cyclophosphamide, doxorubicin, vincristine (CAV), and etoposide cisplatin (EP) delivered either in sequential or alternating sequence, while thoracic radiotherapy was given at different schemes and randomizations [25 Gy in 10 fractions or 37.5 Gy in 15 fractions after CT in BR.3 and 40 Gy in 15 fractions concurrently with EP with randomization to either the early (with cycle 2, week 4) or late (with cycle 6, week 16) arm in BR.6]. In the dose range examined, age does not appear to impact on the delivery, tolerance or efficacy of thoracic radiotherapy in the combined modality management of LD-SCLC (5). The prognostic importance of age on response rate and survival in patients with LD-SCLC was evaluated in a second retrospective analysis concluding that age is not a significant adverse prognostic variable in this cohort of patient and potentially curative combined-modality treatment should not be withheld on the basis of age (6).

The third retrospective analysis reevaluated the Intergroup Trial 0096, a phase III trial comparing EP plus once or twice daily concurrent thoracic radiotherapy in 381 LD-SCLC patients of which 50 (13%) aged over 70 years, to determine the effects of patient age on outcome (7). Age was not found to be associated with response or local control rates. The 5-year survival rates were 16% for elderly compared with 22% for younger patients (P=0.051). Response rate (88% *vs.* 80%; P=0.11), event free survival rate (5 years, 19% *vs.* 16%; P=0.18), time to local failure, and duration of response did not differ between elderly and younger than 70 years groups. However, toxicity, particularly hematologic (grade 4–5: 61% *vs.* 84%; P=0.01) and fatal toxicity (1% *vs.* 10%; P=0.01) was greater among the elderly. The selection of older patients, such as those with a good performance status, should be considered for optimum treatment approaches (7).

The results were quite similar to findings reported in the last retrospective analysis on 54 elderly patients (age ≥70 years old) of a total of 263 patients with LD-SCLC enrolled in another phase III trial launched by the North Central Cancer Treatment Group (NCCTG) to compare EP plus either once daily radiotherapy (QDRT) or split-course BIDRT (8). Despite elderly patients presented more weight loss, poorer performance status, increased pulmonary toxicity, and more deaths due to treatment, their survival was not found to be significantly worse. The 2- and 5-year survival rates were 48% and 22% for younger patients compared with 33% and 17% for older patients (P=0.14). Fit elderly patients with LD-SCLC can receive combined-modality therapy with the expectation of relatively favorable long-term survival (8).

A retrospective study investigated the factors predicting pulmonary toxicity of radiotherapy in SCLC patients in a pooled analysis of three CALGB CRT protocols investigating two cycles of CT followed by concurrent CT and 70 Gy daily thoracic radiation therapy. In the univariate analysis, the authors showed patients who experienced post-treatment pulmonary toxicity were more likely to be older (median age 69 *vs.* 60, P=0.09) (9).

Elderly, infirm, or noncompliant patients with LD-SCLC who are unable to receive standard-duration CT may have useful palliation and potential benefit in survival with abbreviated CT (two cycles) and thoracic radiotherapy. Two phase II trials have been designed specifically for elderly patients with LD-SCLC, which used two cycles of CT in combination with thoracic radiation at low doses and have reported interesting results in terms of activity and tolerability (10,11). In the first trial, 55 LD-SCLC patients (median age, 73) were treated with one cycle of CAV followed 3 weeks later by one cycle of EP. Both regimens were administered at conventional full dose and thoracic irradiation (20 to 30 Gy) was delivered concurrently with EP (10). Abbreviated treatment represents a model of management that potentially can achieve the treatment goals of relief of symptoms, prolongation of median survival, and a chance of cure with acceptable toxicity. Complete response occurred in 28 patients (51%) and partial response in 21 (38%). The median survival for LD-SCLC patients treated with the abbreviated regimen was 54 weeks, shorter than median survival times cited for recently reported studies of combined modality therapy, but similar to a meta-analysis of chemoradiation versus CT alone for LD-SCLC (3). The 2-year survival rate was 28% and 5-year survival rate was 18%.

In the second study, 75 patients, aged ≥70 years with a Karnofsky performance status of ≥60% and no other major medical problems, were treated with a protocol combining only two courses of intravenous carboplatin and oral etoposide with concomitant accelerated hyperfractionated radiation at a dose of 1.5 Gy administered twice daily (total

dose, 45 Gy) (11). This combined treatment program was tolerable and produced promising long term results. Response rate was 75%, and complete response was observed in 57% of the patients. The median survival time was 15 months, and the 2- and 5-year survival rates were 32% and 13%, respectively. Acute grade 3 leukopenia, thrombocytopenia, and esophagitis were observed in 8.3%, 11%, and 2.8% of the patients, respectively. Only one patient experienced grade 4 acute toxicity (thrombocytopenia) (11).

However, the long term survival results obtained in these studies were achieved in a patient population that was largely selected for study.

Moreover, the majority of these trials were conducted in the 90's before the advent of modern CT and radiotherapy regimens, so it is unclear whether the newer combination treatment can potentially reduce the risk of toxicity in elderly patients.

Additional randomized trials have assessed thoracic radiotherapy timing (early, defined as beginning within 30 days after the start of CT, *vs*. late) and sequencing (concurrent *vs*. sequential) in LD-SCLC (12-15). A Japanese phase III trial randomly assigned 228 patients to receive either sequential (after the fourth cycle of EP every 3 weeks) or concurrent radiotherapy (chest radiation begun on day 2 of the first cycle of the same CT administered every 4 weeks) (12). Concurrent radiotherapy yielded better survival than sequential radiotherapy (median OS 27.2 *vs*. 19.7 months), but with more sever hematologic toxicity and severe esophagitis. Another phase III trial confirmed an improved local and systemic control with longer survival with early radiotherapy (started at cycle 2 of CT) compared to late radiotherapy (at cycle 6) (13). A systematic review on the timing of thoracic radiotherapy resulted in a small but significant improvement in OS with early administration of thoracic irradiation in the combined modality therapy when compared with late concurrent or sequential strategy (14). Finally, a more recent meta-analysis established a platinum-based CT concurrently with early chest radiotherapy as the most effective way of combining CRT treatment approach for patients with LD-SCLC, reporting a significantly higher 2- and 5-year rate (2-year OS rate: HR =0.73 and P=0.01; 5-year OS rate: HR =0.65 and P=0.02) (15).

Notably, all these trials were performed in overall LD-SCLC population, with no specific subgroup analysis by age and none was performed only in elderly patients.

Although the median age of patients diagnosed with lung carcinoma is 70 years, elderly patients are under-represented in clinical trial. So, it is important to understand the effects of modern combined-modality therapy in the elderly. Older patients who are functional in terms of the ability to perform activities of daily living should be treated with standard combination therapy (and radiotherapy, if indicated). However, myelosuppression, fatigue, and lower organ reserves are encountered more frequently in elderly patients; therefore they must be watched carefully during treatment to avoid excessive risk (16).

The introduction of new radiotherapy techniques, such as the involved field treatment based on PET imaging, could minimize the risk and the amount of lung and esophageal toxicity. In fact, it was showed that the selective nodal irradiation based on PET-scan positivity reduces treated volume and toxicity without compromising the possibility of local control and cure (17).

Furthermore the continuous diffusion of intensity modulated radiotherapy, even in thoracic treatments with its sartorial capacity of dose distribution, was showed to reduce the rate of toxicity of lung RT, saving not only esophagus and healthy lungs but also bone marrow, so minimizing the hematological toxicity (18). Finally, the recent possibility of intensity modulated treatment synchronized with respiratory movement, the use of 4D CT and 4D cone beam CT, and the introduction of user friendly adaptive radiotherapy software, would mean new possibilities in reducing uninvolved tissue treated volumes and, so, the potential toxicity. The patients, who might benefit most from these new possibilities, will certainly be the frailest ones, as the elderly.

Based on this premise, in the here discussed study Corso *et al*. have recently investigated outcomes for elderly patients treated with CT alone compared to chemoradiotherapy in the modern era (19). Investigators conducted a population-based retrospective analysis using the National Cancer Data Base (NCDB), and identified 8,637 elderly patients (age ≥70 years) with LD-SCLC (defined as clinical stage I to III disease, cT0–T4, cN0–N3, cM0) who were treated with CT (3,775 patients; 43.7%) or CRT (4,862 patients; 56.3%) between 2003 and 2011.

In the entire cohort, median OS was estimated to be 15.6 months (95% CI, 15.2–16.2 months) and 9.3 months (95% CI, 9.0–9.6 months) in CRT and CT group, respectively (P<0.001), with a significant improvement in 3-year OS rate (22.0% *vs*. 6.3%, respectively). This benefit was confirmed also in cohort of patients older than 80 years (mOS and 3-year OS rate: 13.6 months and 16.4% *vs*. 8.1 months and 5.2% for patients receiving CRT and CT,

respectively). CRT provided a similar OS benefit also in the subset of patients with multiple medical comorbidities (P<0.001). A subset analysis restricting the CT cohort to patients for whom RT was explicitly recommended but not delivered (335 of 3,775 patients) was performed to reduce selection bias of this retrospective trial. The survival benefit for CRT persisted, with a median OS and 3-year OS of 15.6 months and 22.0% (unchanged) respectively, compared to 11 months and 10.6% for the cohort of 335 patients receiving CT (19).

Radiotherapy achieved a similar OS, regardless the doses and schedules used (45 Gy in 1.5 Gy fractions or 1.8 to 2.0 Gy fractions to a dose ≥60 Gy) in CRT group (P=0.20), and both regimens improved survival when compared with CT (P<0.001).

The concurrent CRT (defined as starting radiotherapy 30 days before to 60 days after CT began) produced a modest, but significant, long-term benefit (3.9% 3-year OS benefit) for patients compared with a sequential treatment; however the curves crossed approximately at 12 months after diagnosis.

Propensity score matching was performed to identify matched cohorts (6,856 patients; 3,428 each group) representing the two treatment modalities, using the variables found to be independent predictors of OS on multivariable analysis (CRT, age younger than 80 years, female sex, Charlson-Deyo score 0, clinical stage I disease, and receipt of non-single-agent CT). Propensity score matching confirmed a survival benefit of CRT over CT (HR =0.52; 95% CI, 0.50–0.55; P<0.001), with a 3-year OS of 20.6% (95% CI, 19.2–22.1%) for the matched CRT group and 6.6% (95% CI, 5.7–7.5%) for the CT group (19).

Elderly patients represent a particular population, often with concomitant medical problems (comorbidity and reduction of function of various organs and systems) discouraging the choice of optimum treatment and leading to an under-treatment. The "chronological age" should impact less than other variables, such as life expectancy, comorbidities and performance status, on the choice of the better therapeutic strategy. In literature, most of available data concerning CRT derived from retrospective analyzes, usually conducted on small samples of patients, poorly representative of the general elderly population. Furthermore, the discouraging results of combined treatment in LD-SCLC elderly patients come from trials designed about 20 years ago. Recently, any study has assessed the potential benefit resulting from the use of modern conformal radiotherapy techniques and progress made in the field of supportive care. Of course, further phase III trials conducted only on the elderly population could clarify the best therapeutic approach in these patients, representing about 40% of SCLC.

Corso *et al*. (19) try to define the best strategy of treatment in elderly conducting this retrospective analysis on more recent data [2003–2011], although it was weighed by inherent multiple bias and by the lacks information on performance status, on prophylactic cranial irradiation, and on CT regimens used. Notably, they not clarified the reasons why patients treated with CT alone did not receive thoracic radiotherapy, probably unfit to thoracic radiotherapy or with an early disease progression and so never eligible to thoracic irradiation. In effort to reduce selection bias, this retrospective analysis provides a propensity score matching and a subgroup analysis in patients for whom radiotherapy was explicitly recommended but not delivered.

Authors conclude that the age alone should not be exclusion criteria, and that CRT should be the preferred strategy also in elderly patients who are expected to tolerate the toxicities of the combined approach. In the lack of randomized clinical trials, this is the first study suggesting a survival benefit with the concurrent CRT approach compared to the sequential also in elderly.

Therefore, the "biological age" should have a greater importance than "chronological age" in choice of the better therapeutic strategy in the clinical practice.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Editorial commissioned by the Section Editor Melanie He, Science Editor of Translational Lung Cancer Research.
Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Gridelli C, Casaluce F, Sgambato A, Monaco F, Guida C. Treatment of limited-stage small cell lung cancer in the elderly, chemotherapy *vs.* sequential chemoradiotherapy *vs.* concurrent chemoradiotherapy: that's the question. Transl Lung Cancer Res 2016;5(2):150-154. doi: 10.21037/tlcr.2016.03.03

