Editorial Commentary

First-line cytotoxic chemotherapy regimen for non-small cell lung cancer in the elderly population: plus ça change

Grace K. Dy, Maya Khalil, Edwin Yau

Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

Correspondence to: Grace K. Dy. Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA. Email: grace.dy@roswellpark.org.

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article did not undergo external peer review.

Comment on: Okamoto I, Nokihara H, Nomura S, *et al.* Comparison of Carboplatin Plus Pemetrexed Followed by Maintenance Pemetrexed With Docetaxel Monotherapy in Elderly Patients With Advanced Nonsquamous Non-Small Cell Lung Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncol 2020;6:e196828.

Submitted May 01, 2020. Accepted for publication May 14, 2020.

doi: 10.21037/tlcr-2020-15

View this article at: http://dx.doi.org/10.21037/tlcr-2020-15

Amidst all the scientific advancements in the current decade that have led to the widespread use of targeted therapy and immunotherapy as first-line therapy in biomarker-defined non-small cell lung cancer (NSCLC), platinum-based chemotherapy remains one of the core systemic treatment backbones for this disease. However, its administration in the geriatric population pose age-old (no pun intended!) challenges due to the increased prevalence of co-morbid conditions that uniquely predispose this group of patients to frailty and to the increased risks therefrom of treatment-related toxicities, including death, from multi-drug combination treatment regimens (1). Indeed, the youngest patient who was enrolled in TOPICAL, a phase 3 placebo-controlled trial investigating the efficacy of a targeted therapy versus best supportive care in NSCLC patients deemed unsuitable for chemotherapy was 72 years old, with patients >75 years old comprising nearly two-thirds of all subjects enrolled (2). Unfortunately, many of the new treatment standards, including platinum-based regimens, were defined from pivotal clinical trials wherein more than half of the patients enrolled are less than 65 years of age. In contrast, more than half of the prevalent cases of lung cancer between 2010–2015 in the United States are diagnosed in patients 70 years or older (3). This prevalence underscores the importance of clinical trials specifically enrolling the elderly population and is further exemplified by the subsequent observations regarding the lack of survival benefit, the risk of increased toxicities and even concern for increased mortality with certain systemic treatment regimens in older NSCLC patients (4,5).

Data from several studies shed some light on the question of what the most suitable cytotoxic chemotherapy regimen to employ in the first-line treatment of the fit elderly NSCLC patient. Although the pooled analysis by the CISCA meta-analysis group of individual patient data from randomized trials comparing carboplatin to cisplatin favored the use of cisplatin-based regimens particularly in patients with nonsquamous histology and in combination with third-generation cytotoxic chemotherapy agents (6), it is to be noted that more than two-thirds of patients included in the meta-analyses were <65 years. To address whether cisplatin-based combination is better than monotherapy as first-line treatment in the elderly population, the prospective randomized MILES-3 and MILES-4 trials together planned to accrue more than 1,000 NSCLC patients 70 years or older with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, but the studies were terminated due to poor accrual (7). Joint analysis of the study endpoints based on data from 531 patients enrolled in to revealed that even though the addition of cisplatin to gemcitabine for squamous NSCLC or pemetrexed for nonsquamous NSCLC compared to either gemcitabine or pemetrexed alone improved PFS (HR 0.76, P=0.006), the difference in overall survival (OS) was not statistically significant (HR 0.86, P=0.14) (7). It is to be noted though that the original sample size planned for recruitment would

not have been sufficiently powered to detect the hazard ratio encountered at this threshold, much less with the premature termination. Another Japanese phase III trial evaluating the addition of weekly cisplatin to docetaxel in a similar elderly population was also terminated early during the first interim analysis although this time for futility reasons, as OS of the cisplatin-containing arm was inferior to that of docetaxel monotherapy (8). Thus, the prevailing evidence does not lend robust support to the routine use of cisplatin combination in the elderly population.

What about carboplatin? One of the seminal trials that seek to answer whether fit elderly patients derive survival benefit from carboplatin-based combination regimens was completed by Intergroupe Francophone de Cancérologie Thoracique (9). IFCT-0501 compared either vinorelbine or gemcitabine monotherapy to the combination of carboplatin plus weekly paclitaxel in patients 70 years or older with ECOG PS of 0–2. Median age of the patients enrolled was 77 years, with a little over a quarter of patients enrolled having ECOG PS of 2. Despite the expected increase in toxicity with this carboplatin combination, OS was unequivocally better compared to monotherapy. Superior survival was observed across age and PS subgroups. With subsequent analyses of clinical trials demonstrating efficacy and safety profile favoring pemetrexed in the nonsquamous population compared to other agents including taxanes (10,11), subset analysis of the elderly population enrolled in a randomized phase III trial, reported by Pereira *et al*., comparing carboplatin-pemetrexed to carboplatin-docetaxel as first-line treatment in advanced nonsquamous NSCLC showed that although progression-free survival (PFS) and OS were similar between the two regimens, survival without treatment-emergent grade 3 or higher toxicity was significantly better in the pemetrexed-carboplatin group across all age groups, with the magnitude of effect most favoring patients who are >70 years old (12). Notably, this study was completed prior to the establishment of maintenance therapy with pemetrexed as a standard practice (13) and both groups received up to a maximum of 6 cycles of treatment only.

Along this succession of data, the COG1210/WJOG7813L study being discussed in this editorial provides additional context to the existing literature (14). This prospective, multicenter cooperative group study with noninferiority design, specifically randomized 433 nonsquamous NSCLC patients >75 years old with ECOG PS 0–1 in Japan to first-line treatment with carboplatin (area under the curve of 5) and pemetrexed (500 mg/m^2) followed by maintenance pemetrexed in patients without disease progression versus docetaxel (60 mg/m^2) monotherapy administered until disease progression as the control group. Baseline demographic characteristics were well-balanced between the two groups. Notable for this study were that never smokers comprised approximately 40%, and that epidermal growth factor receptor (EGFR)-mutated patients who had previous exposure to EGFR tyrosine kinase inhibitors (TKIs) represented approximately 20%, of patients enrolled in each group.

Results showed that the functional domain of the quality of life assessment in patients was better over time with carboplatin-pemetrexed compared to docetaxel. As expected, higher rates of grade 3 and grade 4 anemia and thrombocytopenia were seen with carboplatin-pemetrexed whereas higher grade 4 neutropenia rate was seen with docetaxel. Although the reported 2-year survival rate favored the carboplatin-pemetrexed group at 40% versus 33.4% in the docetaxel group, the study was not adequately powered to detect this level of difference (i.e., less than 60%). Primary analysis for noninferiority of OS was prespecified to be conducted with Cox proportional hazards model, stratified according to EGFR gene mutation status, stage (IIIB *vs.* IV) and gender. The study met its OS primary endpoint confirming non-inferiority of carboplatin and pemetrexed as first-line therapy in this group of elderly Japanese patients, as the upper limit of the 95% confidence interval (CI) of the stratified hazard ratio (HR) for OS at 1.056 was less than the prespecified margin of 1.154. But this upper bound exceeded 1.0, indicating that superiority of carboplatin-pemetrexed over docetaxel cannot be established, contrary to expectation. However, examination of the Kaplan-Meier (KM) curves for OS reveals that the initial separation of the curves noted through the first 36 months begin to converge around the 40-month time period wherein curves are essentially superimposed thereafter. Contrast this to the KM curves shown in the Pereira *et al*. study which demonstrate superimposed KM curves throughout the entire timeframe under analysis. We can hypothesize that this diminishing value of incorporating carboplatin over time may represent enrollment of patients with uncharacterized favorable prognostic feature in the control group in sufficient numbers to overcome any advantage derived from early carboplatin treatment in the experimental group. What is striking is that the patients enrolled in either treatment group overall had much better estimated 1-year OS at more than 60% compared to estimated 1-year OS rate of 49% in the control group

of patients enrolled in KEYNOTE-189, the randomized placebo-controlled trial that established the superiority of incorporating pembrolizumab with platinum-pemetrexed as first-line therapy in EGFR/ALK wildtype nonsquamous NSCLC compared to platinum-pemetrexed (15). These impressive OS results are similar to the prior WJTOG9904 phase III study of the same docetaxel regimen in a similar Japanese patient population suggesting more favorable prognostic features compared to Western patient populations (16). This may be influenced in part by a sizable proportion of patients enrolled in COG1210/WJOG7813L with potentially better prognosis due to the availability of targeted therapy options for patients with known activating EGFR mutations or for patients who were never smokers who maybe enriched for the presence of other actionable oncogenic mutations sensitive to available targeted therapies. Moreover, this study enrolled patients between 2013 and 2017 which overlapped with the initial commercial use of osimertinib in Japan in 2016 for T790M+ EGFR mutation in the acquired resistance setting to 1st line EGFR TKIs. Although nearly two-thirds of each treatment group received at least 1 subsequent therapy including EGFR TKIs, the type of post-study EGFR TKI or other targeted therapies administered were not reported. Subsequent exposure to osimertinib or other indicated targeted therapy post-study favoring the control group may also contribute to the diminishing value of early treatment with carboplatin as well, although this is purely speculation since information regarding this was not reported. Similarly, given the higher numbers of docetaxel patients receiving subsequent pemetrexed (49%) compared to carboplatin-pemetrexed patients receiving subsequent docetaxel (37.5%), a difference in the efficacy and/or tolerability of subsequent pemetrexed compared to subsequent docetaxel may also dilute the effect of early carboplatin. Lastly, it is to be noted that post-hoc analyses incorporating PS reveal that PFS and OS superiority of the carboplatin-pemetrexed regimen were mainly being driven by patients with ECOG PS of 0 at baseline, with stratified HR for PFS and OS in this group of patients being 0.71 (95% CI, 0.52–0.97) and 0.57 (95% CI, 0.40–0.82), respectively whereas the stratified HR for PFS and OS in patients with ECOG PS 1 were 0.8 (95% CI, 0.62–1.02) and 1.14 (95% CI, 0.87–1.49). In contrast, the IFCT-0501 study showed survival benefit with carboplatin-paclitaxel across all PS, including patients with ECOG PS 2 (9). Differential outcomes arising from genetic variability influenced by ethnicity cannot be excluded and can potentially explain this discrepancy.

In summary, there is indisputable evidence that carboplatin-pemetrexed is an appropriate chemotherapy backbone as first-line therapy in fit elderly patients with nonsquamous NSCLC and COG1210/WJOG7813L provides much needed prospective data in this understudied and very clinically relevant population. Findings from COG1210/WJOG7813L also suggest that a subgroup of elderly patients, at least in Japan, are likely to have long-term survival and do well with non-platinum-containing monotherapy drugs as 1st line chemotherapy. There is thus continued need for further research to understand age-related differences in tumor biology as well as more support to conduct and complete clinical trials dedicated to optimizing treatment decisions for this population of patients with unique physiological characteristics and needs.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr-2020-15). The authors have no conflicts of interests 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.

References

1. Repetto L. Greater risks of chemotherapy toxicity in elderly patients with cancer. J Support Oncol 2003;1:18-24.
2. Lee SM, Khan I, Upadhyay S, et al. First-line erlotinib in patients with advanced non-small-cell lung cancer

unsuitable for chemotherapy (TOPICAL): a double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2012;13:1161-70.
3. Prevalence estimates of patients diagnosed with lung cancer in the United States from 2010 to 2015. Available online: https://gis.cdc.gov/Cancer/USCS/DataViz.html (last accessed April 3, 2020).
4. Zhu J, Sharma DB, Gray SW, et al. Carboplatin and paclitaxel with vs without bevacizumab in older patients with advanced non-small cell lung cancer. JAMA 2012;307:1593-601.
5. Langer CJ, Socinski MA, Patel JD, et al. Isolating the Role of Bevacizumab in Elderly Patients With Previously Untreated Nonsquamous Non-Small Cell Lung Cancer: Secondary Analyses of the ECOG 4599 and PointBreak Trials. Am J Clin Oncol 2016;39:441-7.
6. Ardizzoni A, Boni L, Tiseo M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. J Natl Cancer Inst 2007;99:847-57.
7. Gridelli C, Morabito A, Cavanna L, et al. Cisplatin-Based First-Line Treatment of Elderly Patients With Advanced Non-Small-Cell Lung Cancer: Joint Analysis of MILES-3 and MILES-4 Phase III Trials. J Clin Oncol 2018;36:2585-92.
8. Abe T, Takeda K, Ohe Y, et al. Randomized phase III trial comparing weekly docetaxel plus cisplatin versus docetaxel monotherapy every 3 weeks in elderly patients with advanced non-small-cell lung cancer: the intergroup trial JCOG0803/WJOG4307L. J Clin Oncol 2015;33:575-81.
9. 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.
10. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-51.
11. Scagliotti G, Brodowicz T, Shepherd FA, et al. Treatment-by-histology interaction analyses in three phase III trials show superiority of pemetrexed in nonsquamous non-small cell lung cancer. J Thorac Oncol 2011;6:64-70.
12. Pereira JR, Cheng R, Orlando M, Kim JH, Barraclough H. Elderly subset analysis of randomized phase III study comparing pemetrexed plus carboplatin with docetaxel plus carboplatin as first-line treatment for patients with locally advanced or metastatic non-small cell lung cancer. Drugs R D 2013;13:289-96.
13. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2013;31:2895-902.
14. Okamoto I, Nokihara H, Nomura S, et al. Comparison of Carboplatin Plus Pemetrexed Followed by Maintenance Pemetrexed With Docetaxel Monotherapy in Elderly Patients With Advanced Nonsquamous Non-Small Cell Lung Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncol 2020;6:e196828.
15. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078-92.
16. Kudoh S, Takeda K, Nakagawa K, et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 2006;24:3657-63.

Cite this article as: Dy GK, Khalil M, Yau E. First-line cytotoxic chemotherapy regimen for non-small cell lung cancer in the elderly population: plus ça change. Transl Lung Cancer Res 2020;9(4):1591-1594. doi: 10.21037/tlcr-2020-15

