Editorial

Two's company, three's a crowd: the continuing saga of three-drug regimens for extensive-stage small cell lung cancer

Frank Weinberg, Gregory P. Kalemkerian

Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

Correspondence to: Gregory P. Kalemkerian, MD. Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan, C350 Med Inn – SPC 5848, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-5848, USA. Email: kalemker@umich.edu.

Comment on: Jalal SI, Lavin P, Lo G, *et al.* Carboplatin and etoposide with or without palifosfamide in untreated extensive-stage small-cell lung cancer: a multicenter, adaptive, randomized phase III study (MATISSE). J Clin Oncol 2017;35:2619-23.

Submitted Oct 10, 2017. Accepted for publication Oct 16, 2017.
doi: 10.21037/tcr.2017.10.41
View this article at: http://dx.doi.org/10.21037/tcr.2017.10.41

Small-cell lung cancer (SCLC) is an aggressive tumor that accounts for 13–15% of all lung cancer cases and is the seventh most common cause of cancer-related death in the U.S. with a 5-year overall survival rate of 6.3% (1). At initial diagnosis, about 2/3 of patients have extensive-stage disease (ES-SCLC), for which all treatment is given with palliative intent. Platinum-based, two-drug chemotherapy has been the standard first-line treatment for patients with ES-SCLC for over 20 years. In the U.S., the most common regimens utilized are carboplatin plus etoposide (CE) or cisplatin plus etoposide (PE), which yield a response rate of 50–70% and a median overall survival time of 8–11 months (2). Despite the remarkable activity of initial chemotherapy, nearly all patients relapse within months and the benefits of second-line therapy are limited. Thus, there is a desperate need for more effective first-line therapy.

In an effort to improve the activity of chemotherapy in ES-SCLC, Jalal *et al.* performed a multi-center, randomized, adaptive, global, phase III trial of CE with or without palifosfamide in patients with untreated ES-SCLC (MATISSE) (3). The rational for this study stemmed from the favorable findings of a prior phase III Hoosier Oncology Group (HOG) trial that randomized 171 patients with previously untreated ES-SCLC to PE plus ifosfamide *vs.* PE alone and reported improved overall survival with the addition of ifosfamide (median, 9.0 *vs.* 7.3 months; 2-year, 13% *vs.* 5%; P=0.045) (4). However, the increased toxicity of PE plus ifosfamide limited the adoption of this regimen as standard first-line therapy.

The recently published MATISSE trial aimed to build on the prior HOG experience by incorporating two less toxic drugs: palifosfamide, a less toxic analog derived from the active metabolite of ifosfamide; and carboplatin, which is less toxic than cisplatin. One-hundred eighty-eight eligible patients with previously untreated, ES-SCLC and ECOG performance status 0–2 were randomized in a 1:1 ratio to receive either CE or CE plus palifosfamide (PaCE). Unfortunately, the study failed to meet its primary endpoint of improving overall survival with the addition of palifosfamide since patients assigned to receive PaCE did not have a significant difference in median overall survival as compared to those receiving CE (10.0 *vs.* 10.4 months, P=0.096). Subgroup analysis revealed that there were no statistically significant differences in overall survival between PaCE and CE based on sex, performance status or region of treatment (U.S. *vs.* non-U.S.). However, in patients over 65 years of age, those assigned to receive CE had superior survival when compared to those receiving PaCE (9.7 *vs.* 6.8 months, P=0.044). Toxicity data on this study were not optimally collected, but there were no apparent differences in serious adverse events (CE, 27.5% *vs.* PaCE, 28.3%) or treatment-emergent adverse events (about 20% in each arm) between the treatment arms. Based on the overall results of this study, the authors appropriately concluded that the addition of palifosfamide to CE did not improve the outcome for people with ES-SCLC.

The MATISSE study had several limitations. First, the planned accrual was 464 patients, but the trial was closed after enrolling only 188 patients. This was due to a change in the development plan for palifosfamide after the failure to detect a statistically significant difference in progression-free survival in the phase III PICASSO III trial comparing

palifosfamide plus doxorubicin *vs.* doxorubicin alone in patients with metastatic soft tissue sarcoma (5). While the small sample size in the current study clearly resulted in suboptimal power to detect a statistically significant difference between the treatment arms, the available data demonstrated numerically better overall survival in patients assigned to CE, suggesting that further accrual would be highly unlikely to sway in favor of PaCE.

Second, once the decision was made to discontinue enrollment, data collection was drastically curtailed, a decision that is incompatible with the norms of clinical trial performance and the scientific process. Response assessments were collected in only 45% of patients, making it impossible to calculate accurate response rates. Response rates can be a useful surrogate for clinical benefit and can provide a more comprehensive assessment of the efficacy of a particular treatment approach. The attenuation of data collection also impacted on the ability to fully assess the toxicity of the PaCE regimen, as important parameters such as dose reductions, treatment delays and complete adverse events were not adequately monitored. The appropriate collection and publication of such information would have provided a much more thorough picture of the PaCE regimen and would have assisted in the development of future clinical trials. It is a shame that the commitment made by the 188 patients who enrolled on this trial was not shared by the sponsor.

Finally, the results of the MATISSE trial may not be generalizable to all geographically localized SCLC patient populations given the global accrual with two-thirds of patients enrolled outside the United States. We do know from prior experience that the results of SCLC studies from some countries, particularly Japan, have not been reproducible in American or other western populations (6-8).

Despite the limitations in patient accrual, data collection, and population heterogeneity, it is unlikely that optimization of these factors would have resulted in a positive study. The MATISSE trial confirms the lack of survival benefit with three-drug regimens that has been reported in numerous other studies in patients with ES-SCLC. For example, in CALGB-9732, 587 patients with untreated ES-SCLC were randomized to receive PE or PE plus paclitaxel (PET) with no significant differences noted in response rate (68% *vs.* 75%), failure-free survival (median, 5.9 *vs.* 6.4 months, P=0.18) or overall survival (median, 9.9 *vs.* 10.6 months, P=0.17) (9). However, PET was associated with an unacceptable increase in treatment-related deaths, primarily due to neutropenic sepsis (2.4% *vs.* 6.5%) despite the standard use of G-CSF. On the other hand, a few positive trials with three-drug regimens have been published. The aforementioned HOG study did demonstrate a significant improvement in overall survival with cisplatin, etoposide and ifosfamide, but this came at the cost of increased toxicity which is a common problem with the use of more aggressive regimens in patients with SCLC (4). More recently, a randomized phase III trial from Japan, JCOG0605, compared the three-drug regimen of cisplatin, etoposide and irinotecan (PEI) *vs.* single-agent topotecan as second-line treatment for patients with sensitive-relapsed SCLC and reported a significant increase in overall survival (18.2 *vs.* 12.5 months, P=0.0079) (10). However, the toxicity of the PEI regimen was substantial; febrile neutropenia occurred in 31% of patients receiving PEI *vs.* 7% in the topotecan group, with 50% of patients in the PEI group requiring a dose-reduction and 84% a dose-delay. Overall, the toxicity profile of PEI raised significant concerns about the tolerability of this regimen. In addition, patients in this study had unusually good performance status and survival for patients with relapsed SCLC, raising questions as to the generalizability of the findings (11).

Numerous other chemotherapy-based strategies, including dose-intensification (12), dose-dense regimens (13), weekly administration (14), high-dose consolidation (15), alternating or sequential non-cross-resistant regimens (16), maintenance therapy (17) and consolidation therapy (18), have failed to demonstrate consistent improvements in survival, and several of these approaches have resulted in unacceptable toxicity. Unfortunately, despite the identification of many potential molecular targets and promising preclinical leads, a wide variety of molecularly targeted therapeutic approaches have also failed to generate favorable results in clinical trials (19). Given the unsatisfying outcomes of these alternative treatment strategies, carboplatin or cisplatin plus etoposide still remains the standard of care for patients with ES-SCLC.

Recently, however, there has been a glimmer of hope that advances in targeted therapy and immunotherapy may improve the outcome of patients with SCLC. The most promising molecular approach utilizes rovalpituzumab tesirine (Rova-T), an antibody-drug conjugate consisting of a humanized monoclonal antibody targeting DLL3, a Notch ligand that is overexpressed in SCLC tumor-initiating cells, linked to a DNA damaging toxin. A recently

reported phase I study of Rova-T in heavily pretreated patients with relapsed SCLC noted a response rate of 18% in all 60 patients and 38% in the 26 patients with high DLL3 tumor expression (20). Several studies exploring immune checkpoint inhibitors in patients with ES-SCLC have also shown clinical promise. A randomized, phase II trial comparing carboplatin and paclitaxel plus either ipilimumab, an anti-CTLA-4 monoclonal antibody, or placebo in 164 patients with ES-SCLC demonstrated a higher response rate and a trend toward improved overall survival in those receiving ipilimumab (21). A phase Ib trial of pembrolizumab, an anti-PD1 monoclonal antibody, reported a response rate of 33% in patients with PD-L1-positive SCLC (22). A separate phase I/II study in patients with relapsed SCLC evaluated nivolumab, another anti-PD1 antibody, and the combination of nivolumab plus ipilimumab. Response rates were 10% in the 98 patients treated with single-agent nivolumab and 21% in 115 patients treated with the combination (23). Further clinical trials of immunotherapy in SCLC are currently underway, including trials to assess three-drug regimens of platinum-based chemotherapy plus an immune checkpoint inhibitor. Hopefully, these regimens will be more effective and less toxic than prior three-drug combinations of cytotoxic chemotherapy.

Currently, available treatment options for patients with ES-SCLC are limited and overall prognosis remains poor. Platinum-based, two-drug chemotherapy is still the standard first-line treatment with single-agent chemotherapy or immunotherapy as options upon relapse. The disappointing results of the MATISSE trial once again illustrate the challenges facing the many investigators striving to develop better therapeutic strategies to combat this aggressive and recalcitrant disease.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Wei Xu (Jiangsu Provincial Key Laboratory of Geriatrics, Department of Geriatrics, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.10.41). 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.

References

1. Kalemkerian GP, Schneider BJ. Advances in small cell lung cancer. Hematol Oncol Clin North Am 2017;31:143-56.
2. Kalemkerian GP, Hayman JA. Management of extensive-stage small cell lung cancer. In: Kalemkerian GP, Donington JS, Gore EM, et al. editors. The Handbook of Lung Cancer and Other Thoracic Malignancies. New York: Demos Medical, 2016:223-46.
3. Jalal SI, Lavin P, Lo G, et al. Carboplatin and etoposide with or without palifosfamide in untreated extensive-stage small-cell lung cancer: a multicenter, adaptive, randomized phase II study (MATISSE). J Clin Oncol 2017;35:2619-23.
4. Loehrer PJ Sr, Ansari R, Gonin R, et al. Cisplatin plus etoposide with and without ifosfamide in extensive small-cell lung cancer: a Hoosier Oncology Group study. J Clin Oncol 1995;13:2594-9.
5. Ryan CW, Merimsky O, Agulnik M, et al. PICASSO III: A phase III, placebo-controlled study of doxorubicin with or without palifosfamide in patients with metastatic soft tissue sarcoma. J Clin Oncol 2016. [Epub ahead of print].
6. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 2002;346:85-91.
7. Hanna N, Bunn PA Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage small-cell lung cancer. J Clin Oncol 2006;24:2038-43.

8. Lara PN Jr, Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 2009;27:2530-5.
9. Niell HB, Herndon JE 2nd, Miller AA, et al. Randomized phase III Intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B trial 9732. J Clin Oncol 2005;23:3752-9.
10. Goto K, Ohe Y, Shibata T, et al. Combined chemotherapy with cisplatin, etoposide, and irinotecan versus topotecan alone as second-line treatment for patients with sensitive relapsed small-cell lung cancer (JCOG0605): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2016;17:1147-57.
11. Qin A, Kalemkerian GP. Cisplatin, etoposide, and irinotecan for relapsed small-cell lung cancer. Transl Cancer Res 2016;5:S1142-4.
12. Leyvraz S, Pampallona S, Martinelli G, et al. A threefold dose intensity treatment with ifosfamide, carboplatin, and etoposide for patients with small cell lung cancer: a randomized trial. J Natl Cancer Inst 2008;100:533-41.
13. Lorigan P, Woll PJ, O'Brien ME, et al. Randomized phase III trial of dose-dense chemotherapy supported by whole-blood hematopoietic progenitors in better-prognosis small-cell lung cancer. J Natl Cancer Inst 2005;97:666-74.
14. Furuse K, Fukuoka M, Nishiwaki Y, et al. Phase III study of intensive weekly chemotherapy with recombinant human granulocyte colony-stimulating factor versus standard chemotherapy in extensive-disease small-cell lung cancer. J Clin Oncol 1998;16:2126-32.
15. Elias A, Ibrahim J, Skarin AT, et al. Dose-intensive therapy for limited-stage small-cell lung cancer: long-term outcome. J Clin Oncol 1999;17:1175.
16. Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol 1992;10:282-91.
17. Rossi A, Garassino MC, Cinquini M, et al. Maintenance or consolidation therapy in small-cell lung cancer: a systematic review and meta-analysis. Lung Cancer 2010;70:119-28.
18. Schiller JH, Adak S, Cella D, et al. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593--a phase III trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2001;19:2114-22.
19. Schneider BJ, Kalemkerian GP. Personalized therapy of small cell lung cancer. Adv Exp Med Biol 2016;890:149-74.
20. Rudin CM, Pietanza MC, Bauer TM, et al. Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. Lancet Oncol 2017;18:42-51.
21. Reck M, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol 2013;24:75-83.
22. Ott PA, Elez E, Hiret S, et al. Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the phase Ib KEYNOTE-028 study. J Clin Oncol 2017;35:3823-9.
23. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilumumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open label, phase 1/2 trial. Lancet Oncol 2016;17:883-95.

Cite this article as: Weinberg F, Kalemkerian GP. Two's company, three's a crowd: the continuing saga of three-drug regimens for extensive-stage small cell lung cancer. Transl Cancer Res 2017;6(Suppl 9):S1414-S1417. doi:10.21037/tcr.2017.10.41.

