



Relapsed small cell lung cancer: is more better?

Vinicius Ernani¹, Apar Kishor Ganti^{2,3}

¹Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, USA; ²Department of Internal Medicine, VA Nebraska Western Iowa Health Care System, Omaha, NE, USA; ³Division of Oncology-Hematology, University of Nebraska Medical Center, Omaha, NE, USA
Correspondence to: Apar Kishor Ganti, MD, MS, FACP. Division of Oncology-Hematology, University of Nebraska Medical Center, 987680 Nebraska Medical Center, Omaha, NE, USA. Email: aganti@unmc.edu.

Comment on: 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.

Submitted Nov 18, 2016. Accepted for publication Nov 29, 2016.

doi: 10.21037/tcr.2016.12.74

View this article at: <http://dx.doi.org/10.21037/tcr.2016.12.74>

Small cell lung cancer (SCLC) is a very aggressive and complex disease representing approximately 12% to 15% of all lung cancers (1). More than 90% of patients diagnosed with this disease are elderly, current or former heavy smokers (2). SCLC is characterized by rapid growth, early metastasis, and excellent initial response to chemotherapy and radiation (3). The dramatic response to frontline chemotherapy and radiation, unfortunately, contrasts with its subsequent disappointing responses in the relapsed setting. Patients with recurrent disease have a dismal survival of approximately 5 months when treated with chemotherapy (4). Topotecan is the only second-line drug approved by the Food and Drug Administration (FDA) in the United States. Response rate (RR) to topotecan are highly dependent on the progression-free survival (PFS) after frontline platinum-based therapy, reaching 25% in patients who relapsed >3 months (sensitive disease) after front-line therapy and <10% for those whose disease relapsed <3 months from initial platinum-based treatment (5).

The JCOG0605 study published in *Lancet Oncology* was a multicenter phase III randomized trial, comparing cisplatin plus etoposide plus irinotecan with the standard topotecan monotherapy in patients with SCLC with a sensitive relapse (6). The major eligibility criteria included: sensitive relapse (>90 days from the initial platinum-based chemotherapy or chemoradiotherapy); Eastern Cooperative Oncology Group (ECOG) performance status 0–2; and adequate organ function. Patients were randomized 1:1 to receive either topotecan or cisplatin plus etoposide plus irinotecan with growth factor support (combination

chemotherapy). A total of 180 patients were enrolled, 90 assigned to each treatment group. The primary endpoint of overall survival (OS) was significantly longer in the combination chemotherapy group (median 18.2 months) compared to the topotecan group [12.5 months; hazard ratio (HR) 0.67; 90% CI, 0.51–0.88; P=0.0079]. RR was dramatically higher in the combination chemotherapy group (84% *vs.* 27%; 95% CI, 0.22–0.46; P<0.0001). The most common grade 3 or 4 adverse events were neutropenia (83% in the combination chemotherapy group *vs.* 86% in the topotecan group), anemia (84% *vs.* 28%), leucopenia (80% *vs.* 51%), febrile neutropenia (31% *vs.* 7%), and thrombocytopenia (41% *vs.* 28%). Serious adverse events were reported in 4% of patients in the topotecan group and 10% in the combination chemotherapy group. The results of this trial led the authors to conclude that the combination of cisplatin, etoposide, and irinotecan should be the new standard of care for selected patients with sensitive relapsed SCLC.

The study presented by Goto *et al.* met the primary endpoint of OS in patients with sensitive relapse SCLC (6). However, these results need to be analyzed closely prior to making a generalized recommendation in all relapsed SCLC patients. The first aspect to highlight is the highly selective population enrolled in this study, as demonstrated by almost 60% of the patients in the combination arm having an ECOG performance status of 0, compared to 44% in the topotecan arm. In addition, in the combination arm patients had a longer time to relapse/progression after platinum-based therapy compared to the patients in

the topotecan arm (181 vs. 148 days, respectively). Even after selecting healthier patients, the toxicity associated with the combination arm was very concerning. Of note, grade 3 or worse neutropenia and febrile neutropenia were reported in 83% and 31% patients receiving combination chemotherapy, respectively.

Lastly, can the results of this study be applied to the Caucasian population? In 2002, Noda *et al.* published the results of a phase III trial performed in Japan that compared irinotecan plus cisplatin to etoposide plus cisplatin in patients with newly diagnosed ES-SCLC (7). The median survival was 12.8 months in the irinotecan plus cisplatin and 9.4 months in the etoposide plus cisplatin arm ($P=0.002$). Subsequently, 2 large randomized trials done in the United States comparing cisplatin/etoposide to cisplatin/irinotecan in treatment naïve ES-SCLC failed to demonstrate a significant survival difference between the arms (8,9). A plausible explanation for the different outcomes in the Japanese and North America results is the genetic variability, and pharmacodynamics between these ethnic groups.

Therefore, although there is a significant survival advantage seen with the combination of cisplatin, etoposide and irinotecan, the combination appears to be associated with increased toxicity; nonetheless it could still be an option for highly selected, young, fit, Asian patients with sensitive-relapse SCLC. Given previous experiences with discordant results using an irinotecan based regimen, caution should be taken to generalize the results into a standard second-line treatment for sensitive-relapse.

Unfortunately, the therapeutic options for SCLC have remained unchanged over the last 30 years (10). Despite the heterogeneity and high incidence of mutations in SCLC, no targeted therapy has shown to benefit these patients. More recently, however, the use of immunotherapy has entered into the treatment arsenal to tackle cancer. A phase I/II trial (CheckMate 032) assessed the activity and safety of nivolumab and ipilimumab in 216 patients with SCLC who progressed after one or more lines of therapy. RR was 18% with nivolumab monotherapy and 23% with nivolumab/ipilimumab. The median OS was 4.4 months with monotherapy (95% CI, 2.9–9.4) and 8.2 months with combination therapy [(95% CI, 3.7–not reached)]. Treatment was well tolerated with safety profiles similar to that observed in other diseases (11). Another exciting study presented at ASCO by Rudin *et al.* evaluated a first-in-human antibody-drug conjugate against delta-like protein 3 (DLL3), rovalpituzumab tesirine (Rova-T) (12).

The trial included 74 patients with SCLC that had progressed on at least one prior therapy. In DLL3 overexpressors ($\geq 50\%$ of cells expressing DLL3), the RR was 55%. The most common grade 3 and higher toxicities were thrombocytopenia 12%, serosal effusions 11%, and skin reactions 8%. A phase II trial using Rova-T in the 3rd line setting is currently enrolling (TRINITY trial). The combination of Rova-T and nivolumab in the front-line setting is also on the horizon and will be explored in the near future.

In summary, after 30 years of dismal progress in the treatment of SCLC, we are finally starting to see some light at the end of the tunnel. The checkpoint inhibitors (nivolumab and ipilimumab) and Rova-T are exciting novel agents studied in the second-line and beyond. They are also characterized by manageable toxicity profiles, which is essential in the palliative scenario. For now, initial management for SCLC continues to be driven by platinum based-therapy and second-line remains topotecan, but hopefully not for much longer.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Shaohua 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.2016.12.74>). 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.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the

original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

- Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol* 2006;24:4539-44.
- Devesa SS, Bray F, Vizcaino AP, et al. International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. *Int J Cancer* 2005;117:294-9.
- van Meerbeeck JP, Fennell DA, De Ruyscher DK. Small-cell lung cancer. *Lancet* 2011;378:1741-55.
- von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol* 1999;17:658-67.
- Simos D, Sajjady G, Sergi M, et al. Third-line chemotherapy in small-cell lung cancer: an international analysis. *Clin Lung Cancer* 2014;15:110-8.
- 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.
- 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.
- 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.
- 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 disease small-cell lung cancer. *J Clin Oncol* 2006;24:2038-43.
- Oze I, Hotta K, Kiura K, et al. Twenty-seven years of phase III trials for patients with extensive disease small-cell lung cancer: disappointing results. *PLoS One* 2009;4:e7835.
- Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol* 2016;17:883-95.
- Rudin CM, Pietanza MC, Bauer TM, et al. Safety and efficacy of single-agent rovalpituzumab tesirine (SC16LD6.5), a delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC) in recurrent or refractory small cell lung cancer (SCLC). *J Clin Oncol* 2016;34:LBA8505.

Cite this article as: Ernani V, Ganti AK. Relapsed small cell lung cancer: is more better? *Transl Cancer Res* 2016;5(Suppl 7):S1363-S1365. doi: 10.21037/tcr.2016.12.74