Commentary

Second line treatment of small cell lung cancer: more is better?

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Submitted Oct 01, 2016. Accepted for publication Oct 08, 2016.
doi: 10.21037/atm.2016.10.68
View this article at: http://dx.doi.org/10.21037/atm.2016.10.68

Extensive stage small cell lung cancer (SCLC) is an aggressive disease that leaves less than 10% of patients alive at 2 years (1). The mainstay of therapy for extensive stage SCLC is chemotherapy and although the majority of patients will respond to initial chemotherapy, essentially all patients will relapse. Currently there are limited options for treating patients in the second line for both limited and extensive stage disease. The most common second line therapy, topotecan, results in superior survival compared to best supportive care in a phase III clinical trial (2) and has similar outcome compared to combination chemotherapy (3). However, one of the most important factors impacting efficacy of and outcome after second line chemotherapy for SCLC is whether there is progression during initial chemotherapy (refractory disease) and, if not, the interval of time between the end of initial treatment and progression of disease (i.e., relapse) (4,5). Patients with refractory disease or relapse within three months (platinum refractory) not only have a shorter overall survival, but also they are very unlikely to respond to approved second line therapy. In contrast, patients who relapse after 3 months (platinum sensitive) have a clinically meaningful probability of response to chemotherapy, even when the same chemotherapy regimen is reused. Thus, prospective new treatments of SCLC are often tested in two populations: patients with platinum refractory and those with platinum sensitive relapse.

A recently published study by Goto *et al*. further addresses the role of multiagent chemotherapy in platinum sensitive relapse (6). The JCOG0605 study was a phase III randomized, open-label, multicenter trial conducted in Japan that randomized 180 patients with platinum sensitive relapse to either single agent intravenous topotecan or a combination of cisplatin, etoposide, and irinotecan. The study met its primary endpoint of overall survival with a hazard ratio of 0.67, which is very clinically meaningful. However, although the study had a positive result, further consideration is required before it is applied to general practice.

First, as only patients with platinum sensitive disease were included, the result should not be extended to those patients who relapse before 90 days. Meta-analyses of other studies have shown no clinically meaningful benefit for these refractory patients with both single drug and combination chemotherapy (5). The response rate in platinum sensitive disease improves with increasing interval relapse-free interval beyond 90 days. Thus, patients who relapse 6 months do better in terms of both responses to chemotherapy as well as their overall survival, and those who relapse after 2 years have outcomes similar to untreated patients (7). The median time to relapse in the Goto *et al*. study favored the combination chemotherapy group (6 months) compared to topotecan (5 months) with about a quarter of patients in each group relapsing between 3 and 4 months. Whether the benefit was observed in patients regardless of when they relapsed is not clear from the information presented. It may be that only patients relapsing beyond 6 months benefit. Consistent with the relatively long median time to relapse and overall good functional status is the uncharacteristically long median survival in the topotecan group, which had a median survival of 12.5 months (about 54 weeks). Two prior randomized trials of topotecan had survival times of about 25 weeks, making the control group in this current trial survive about twice as long (2,3). Although patients with a performance status of ECOG 2 were included, only 5 pts of 180 entered onto the trial thus the result is poorly applied to patients with worse performance status. Therefore, this current

JCOG trial included healthy patients with much better than average prognosis of relapsed SCLC.

A second factor that needs to be considered is the geographic origin of the population tested. Although SCLC is an almost exclusively smoking related disease, differential outcomes to chemotherapy have been reported across racial groups, in particular among those of Japanese descent as in the Goto study. First line therapy for SCLC has been extensively studied. In two trials, the two-drug regimen cisplatin and etoposide was shown to have an equivalent or better overall survival and improved side effect profile compared to a three-drug regimen of cyclophosphamide, doxorubicin, and vincristine (8,9). Subsequently, cisplatin with etoposide was compared with cisplatin with irinotecan in a Japanese population (10). This trial showed a survival benefit favoring cisplatin with irinotecan. Spurred by this exciting result, two trials were conducted in Europe and America using the same chemotherapy doublet combinations. Unfortunately, both trials showed that cisplatin with irinotecan was essentially equivalent to cisplatin with etoposide (11,12). Also since irinotecan has a worse side effect profile than etoposide including much more symptomatic diarrhea and neutropenia, its use is currently limited in the North American and European population. However the results suggest that there are intrinsic differences in SCLC in a Japanese patient compared to the same cancer in others patients, and may include differences in drug transport gene polymorphisms (12). Therefore, the survival benefit of the irinotecan-containing combination chemotherapy in the Goto trial may have resulted because Japanese patients with SCLC are more likely to respond to irinotecan than other topoisomerase inhibitors, an effect that may not be generalizable to non-Japanese patients (6). Consistent with this hypothesis is the observation that the benefit of the three-drug regimen in JCOG0605 was limited to those patients who had not been previously treated with irinotecan during initial chemotherapy. That is, Japanese patients benefit from irinotecan whether it is used in first line or second line, but appear to derive no additional benefit when irinotecan use is repeated.

Further illustrating the importance of consideration of population variability in therapeutic efficacy is the example of amrubicin, an anthracycline agent whose mechanism of action is mediated by topoisomerase II inhibition rather than DNA intercalation. Amrubicin was studied in a randomized phase II trial in Japan in comparison to topotecan for second line chemotherapy in patients with both platinum sensitive and refractory disease (13). The primary endpoint of this small 60 patient trial, overall response rate, was 38% for amrubicin versus 13% with topotecan (P=0.039). These promising results were confirmed in other trials showing response rates of amrubicin of 36–52%, which led to a phase III trial in comparison to topotecan in Europe and North America and stratified patients as being either platinum sensitive or refractory (14). Amrubicin did not improve overall survival (HR =0.880; P=0.17) in the intention to treat population, though there appeared to be an overall benefit (HR =0.766; P=0.047) in patients with platinum refractory disease. Thus, amrubicin is available (and active based on multiple phase II studies) in Japanese patients but does not improve survival among European and North American populations.

In addition to the direct clinical nuances discussed above, the Goto *et al*. trial and triplet combination chemotherapy should be considered in the context of recent advances in second line therapy of SCLC using immunotherapy. Whereas the survival curves of the patients in the JCOG0605 trial do not appear to have a plateau (30% survival at 2 years and 10% at 3 years), trials of check-point inhibitors in several cancer types (melanoma, NSCLC) asymptotically approach a non-zero survival rate. Published in the same journal, *Lancet Oncology*, 1 month prior was a phase I/II trial of nivolumab combined with ipilimumab in the second line setting (15). If a similar phenomenon is observed in SCLC, the 30% 2 years survival with nivolumab and ipilumumab might be expected to persist beyond 2 years and thus improve overall survival for this highly resistant tumor. Additionally, immune therapy results in improved side effect profile with a 20–30% rate of grade 3/4 toxicities in combination immune therapy compared to an 80% rate of those toxicities in the combination chemotherapy group. Other directions are still being identified in the hope that toxic chemotherapies will be avoided in favor of other less toxic targeted therapies. Lastly, since this is a population almost exclusively made up of tobacco smokers, tobacco cessation needs to be emphasized by all providers as this is a simple cost effective way to improve patients' health and improve their survival.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Commentary commissioned

by Section Editor Jianrong Zhang, MD (Department of Thoracic Surgery, First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease, Guangzhou, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

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.

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Cite this article as: Humeniuk MS, Kelley MJ. Second line treatment of small cell lung cancer: more is better? Ann Transl Med 2016;4(Suppl 1):S65. doi: 10.21037/atm.2016.10.68

