Editorial Commentary

Implications for practice: phase II/III trial of carboplatin and irinotecan for elderly patients with extensive-stage small-cell lung cancer in Japan

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Comment on: Shimokawa T, Okamoto H, Machida R, *et al.* Carboplatin and irinotecan (CI) *vs.* carboplatin and etoposide (CE) for the treatment of extended-stage small-cell lung cancer in an elderly population: A phase II/III randomized control trial. Lung Cancer 2023;181:107195.

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Introduction

Small-cell lung cancer (SCLC) is a high-grade neuroendocrine carcinoma characterized by loss of tumor suppressors RB1 and TP53, activation of MYC, and increased Notch signaling which results in rapid tumor growth and early metastatic spread (1). With 250,000 new cases and 200,000 deaths annually, SCLC makes up about 15% of total lung cancers globally (2,3). Most patients diagnosed with SCLC are current or past heavy smokers (1). SCLC afflicts more men than women, reflecting tobacco use trends (3). The proportion of elderly patients over age 70 years with SCLC has increased in the last 35 years, from 23% in 1975 to 44% in 2010 (4). Approximately two-thirds of patients are diagnosed with extensive stage disease (ES-SCLC) on presentation. Extensive stage disease is defined as disease that cannot be treated within one radiation field or disease with distant metastases (5). Targetable mutations in kinase genes are uncommon, unlike in non-small cell lung cancer (NSCLC) in which biologic therapies can be effective (5). However, SCLC can be classified into biologically distinct subtypes based on transcription factors: ASCL1, NEUROD1, POU2F3, and YAP1 or inflamed subtype SCLC-I, the latter of which may be more susceptible to immunotherapy treatment (6).

History of SCLC treatment

For decades, platinum plus etoposide was the standard of care for ES-SCLC. Although there is an initial high rate of response to chemotherapy, that response is not durable and resistance to chemotherapy inevitably develops, leading to a median overall survival (OS) of less than one year. Numerous trials comparing platinum/etoposide to cyclophosphamide/doxorubicin/vincristine (CAV), cyclophosphamide/epirubicin/vincristine (CEV), doxorubicin/cyclophosphamide/etoposide (ACE), and carboplatin/pemetrexed did not show alternative treatment superiority, maintaining platinum/etoposide as the treatment of choice (7).

In Japan, cisplatin/irinotecan (CDDPI) is considered to be an acceptable first-line treatment for SCLC in younger patients (7). In the JCOG9511 phase II clinical trial comparing the use of CDDPI to cisplatin/etoposide (CDDPE) in 154 patients age 70 years and younger, the median OS was 12.8 months in the CDDPI group versus 9.4 months in the CDDPE group (P=0.002) and the

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landmark survival rate was 58.4% and 37.7% at one year, respectively (8). Confirmatory trials done outside of Japan did not show superiority of CDDPI to CDDPE (7). A meta-analysis on randomized trials for ES-SCLC demonstrated that platinum/irinotecan minimally improved OS over platinum/etoposide while examining four Western population trials [hazard ratio (HR) =0.87; P=0.02] with significantly more diarrhea, but less hematologic toxicity (9). In the current clinical trial, Shimokawa *et al.* sought to determine the efficacy of carboplatin/irinotecan (CI) versus carboplatin/etoposide (CE) in an elderly population of Japan residents (age 71 years and older) given the success of CI in a younger Japanese population (10).

Current standard of care for SCLC

Immunotherapy has changed the landscape of SCLC treatment as it works to boost the activity of T cells against cancer cells by blocking programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) (3). Given that SCLC tends to have a high tumor mutational burden, it stimulates a robust T-cell response, making immunotherapy effective (PD-L1 inhibitors in particular). While the addition of immunotherapy to chemotherapy in the treatment of SCLC has improved OS compared to chemotherapy given alone, the benefit remains modest (11,12).

Two phase III trials, IMpower133 and CASPIAN, showed improved OS with the addition of anti-PD-L1 immunotherapy to chemotherapy for ES-SCLC and both trials led to approvals of chemotherapy plus immunotherapy regimens, which are now considered standard of care in both the United States and Japan. IMpower133 was a multinational study that randomized 403 patients with ES-SCLC in a 1:1 ratio to receive carboplatin and etoposide with either atezolizumab or placebo for four cycles followed by maintenance with atezolizumab or placebo based on what they received in induction (11). Thirty-five point three percent in the atezolizumab arm and 36.6% of patients in the placebo arm were between age 65 and 74 years, 9.5% and 10.9% were age 75 years and older, respectively. About 20% of the participants lived in the Asia-Pacific and 17.8% of the patients were Asian. The median OS was 12.3 months in the atezolizumab group versus 10.3 months in the placebo group [HR =0.70; 95% confidence interval (CI): 0.54–0.91, P=0.007] (11). In the age subgroup analysis, the OS benefit was not statistically significant for patients younger than 65 years (HR =0.92, 95% CI: 0.64–1.32) but was statistically significant for patients age 65 years and older (HR =0.53, 95% CI: 0.36–0.77).

CASPIAN was another multinational study that randomized 805 patients to receive either platinum + etoposide, platinum + etoposide + durvalumab, or platinum + etoposide + durvalumab + tremelimumab in 1:1:1 fashion. Cross-over was not allowed. Thirty-eight percent in the durvalumab arm and 42% of patients in the chemotherapy arm were over the age of 65 years; 13% and 16% were of Asian descent, respectively. For patients living in Asia, there was no statistically significant difference in OS between those that received durvalumab + chemotherapy versus those that received chemotherapy alone (HR =0.81, 95% CI: 0.51–1.29). There was also no statistically significant difference for patients over the age of 65 years (HR =0.90, 95% CI: 0.69–1.19). Forty-two percent and 44% of total patients, respectively, received subsequent treatment (12). In the three-year updated analysis, the median OS was 12.9 months in the durvalumab group versus 10.5 months in the chemotherapy group (HR =0.71; 95% CI: 0.60–0.86, P=0.0003) (13).

KEYNOTE-604 showed a statistically significant progression-free survival (PFS) improvement with the addition of pembrolizumab to platinum/etoposide but only by 0.2 months (14). While OS was 10.8 months in the pembrolizumab group versus 9.7 months in the placebo group, this difference was not significant based on the statistical design (5,14).

The current standard of care for first-line treatment of SCLC in Japan includes atezolizumab + carboplatin + etoposide, durvalumab + cisplatin/carboplatin + etoposide, or cisplatin + irinotecan (15). Cisplatin + irinotecan is considered standard of care in patients who are 70 years old and younger while carboplatin and etoposide is considered standard of care in patients 71 years old and older. In one retrospective study in Japan, platinum plus etoposide was used in 71.4% of patients while platinum plus irinotecan was used in 28.1% for first-line treatment of ES-SCLC (16).

Carboplatin and irinotecan versus carboplatin and etoposide in elderly patients of Japan with ES-SCLC

In the clinical trial reported by Shimokawa *et al.*, 256 patients over age 70 years with ES-SCLC and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 2 were randomized in a 1:1 manner to receive CE or CI (10). The trial accrued patients between 2013 and 2019. Due

to slow accrual, the sample size was decreased from the originally planned 370 patients. The median age of patients was 75 (range, 71–90) years. While patients were mostly randomized evenly between subgroups, there were 10 patients who never smoked in the CE group versus two patients in the CI group. The initial phase II portion of the trial met the objective response rate (ORR) threshold for continuation to the phase III trial. The primary endpoint for the phase III trial was OS while secondary endpoints included PFS, ORR, adverse events, and symptom scores. The median OS was 12 months in the CE arm versus 13.2 months in the CI arm (HR =0.85, 95% CI: 0.65–1.11), and the median PFS was 4.4 months in the CE arm versus 4.9 months in the CI arm (HR =0.85, 95% CI: 0.66–1.09). While CI had a numerically higher PFS and OS than CE, these differences were not statistically significant. As seen in prior studies, there were higher rates of anorexia, nausea, and diarrhea with irinotecan use.

The authors address important limitations in the clinical trial. Their trial started before the immunotherapy trials listed above. Due to slow accrual, the study changed the statistical assumptions to decrease power and shorten the assumed median OS in the control arm by 0.5 to 10.5 months. These changes, especially given the control arm outperformed their assumptions, may have decreased the ability to detect a difference between the two arms of the study. In addition, the authors comment on the effects of post-treatment regimens on outcomes from the study. Amrubicin was used as second-line therapy relatively equally in both arms of the study. Amrubicin is commonly used for the treatment of refractory SCLC in Japan (17). The authors state that the high use of amrubicin in both arms may be a reason the primary endpoint of OS was not met. It is possible that the efficacy of amrubicin in the second-line setting skewed the results to show no statistically significant difference in OS. PFS, however, was also not significantly different between the two cohorts. Of note, there was a large difference in percentage of patients that received CI in the second line setting (1.6% in the CE group versus 9.3% in the CI group). This may also be contributing to differences in OS.

Implications for clinical practice

Overall, the results of Shimokawa *et al.* are not practice changing for the treatment of ES-SCLC and platinum, etoposide and either atezolizumab or durvalumab remains the standard of care based on the IMpower133 and CASPIAN trials. Contrary to previous data in a younger Japanese population, this trial did not demonstrate superior OS with CI in an elderly patient population. Interestingly, despite this being an older patient population without immunotherapy use, the OS from this trial was similar to that in the IMpower133 and CASPIAN trials (11,13). The largest difference between the trials includes the population of patients and where they reside—IMpower133 and CASPIAN were both multinational studies (including Japan) and the trial conducted by Shimokawa *et al.* only included Japanese residents. The different populations may account for differences in OS.

While there were similar trials conducted in Europe, among all age groups, it is difficult to assess whether the results of those trials are similar to the results of Shimokawa *et al.* as no subgroup analysis for age was done. In one trial conducted in Sweden and Norway, CI appeared to increase OS over CE with 30% of patients in the CI arm and 40% of patients in the CE arm being over the age of 70 years (18). In another clinical trial conducted in Germany, there was no statistically significant difference in OS among patients who received CI compared to those that received CE. While these results are similar to the results of Shimokawa *et al.*, they are not consistent with the JCOG9511 trial done in younger patients (19).

It is unclear whether using an age cutoff of 70 years is the best method to determine the best treatment regimen. The presumed rationale for excluding older patients from the original JCOG9511 trial was to avoid toxicity that older individuals may experience. There are likely better measures of fitness to tolerate chemotherapy than age alone. PS, comorbidities such as impaired renal function, or ideally more detailed geriatric assessments may be better criteria for selecting chemotherapy regimens than age alone (20).

Although CE plus immunotherapy remains the standard of care, the ideal regimen for patients in Asia remains unclear at this time. In CASPIAN, there was no statistically significant difference in OS between those that received durvalumab plus chemotherapy versus those that received chemotherapy alone in Asia (HR =0.81, 95% CI: 0.51–1.29). There was also no statistically significant difference for patients over the age of 65 years (HR =0.90, 95% CI: 0.69–1.19). It is not known whether an irinotecan-based regimen in combination with immunotherapy, especially in Japanese patients younger than age 71 years, would be more beneficial than a CE chemotherapy backbone with immunotherapy. Further clinical trials should be conducted to investigate what is the best regimen for patients with ES-SCLC from different age groups, race, and geographic regions.

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