Advances in systemic treatment of small-cell lung cancer including immunotherapy

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Abstract

Small-cell lung cancer (SCLC) shows the rapid clinical course in lung cancer. Median survival times have prolonged with improved management of patients.

In patients with extended disease (ED)-SCLC patients, cisplatin and etoposide had been as a standard treatment. Based on JCOG 9511 and following meta-analyses, cisplatin and irinotecan has also become standard in patients under 70 especially in Japan. Impower133 study results showed significantly longer overall survival in patients received carboplatin, etoposide and atezolizumab than carboplatin and etoposide. Standard treatment for limited disease (LD)-SCLC patients is regarded as cisplatin and etoposide with concurrent chemoradiotherapy. JCOG 0202 was conducted to compare cisplatin + irinotecan and cisplatin + etoposide as the consolidation therapy after chemoradiotherapy. The overall survival from randomization did not differ between the two groups. Cisplatin + etoposide still remain standard treatment method for LD-SCLC.

A lot of treatment methods including immunotherapy for SCLC are under clinical trial as promising treatment option. The choice of treatment should be determined based on a good communication with patients.

Keywords: small-cell lung cancer; ED-SCLC; LD-SCLC; immune checkpoint inhibitor; IMpower133

Introduction

Small-cell lung cancer (SCLC) shows rapid clinical course compared with non-small cell lung cancer (NSCLC). Speed is the most important factor for diagnosis and treatment. State of the art regarding SCLC treatment was first reported by Aisner and colleagues in 1983 [1)]. Median overall survivals were reported as 14 months in limited disease (LD)-SCLC, and 7 months in extensive disease (ED)-SCLC patients. 3-year survival was reported as 15-20% in LD-SCLC and 0% in ED-SCLC patients.

In our manuscript published in 2017 [2)], we described progress of SCLC therapy based on clinical trial results so far. In this updated manuscript, we add information especially about immunotherapy and future perspectives in patients with SCLC.

ED-SCLC

First-line combination chemotherapy

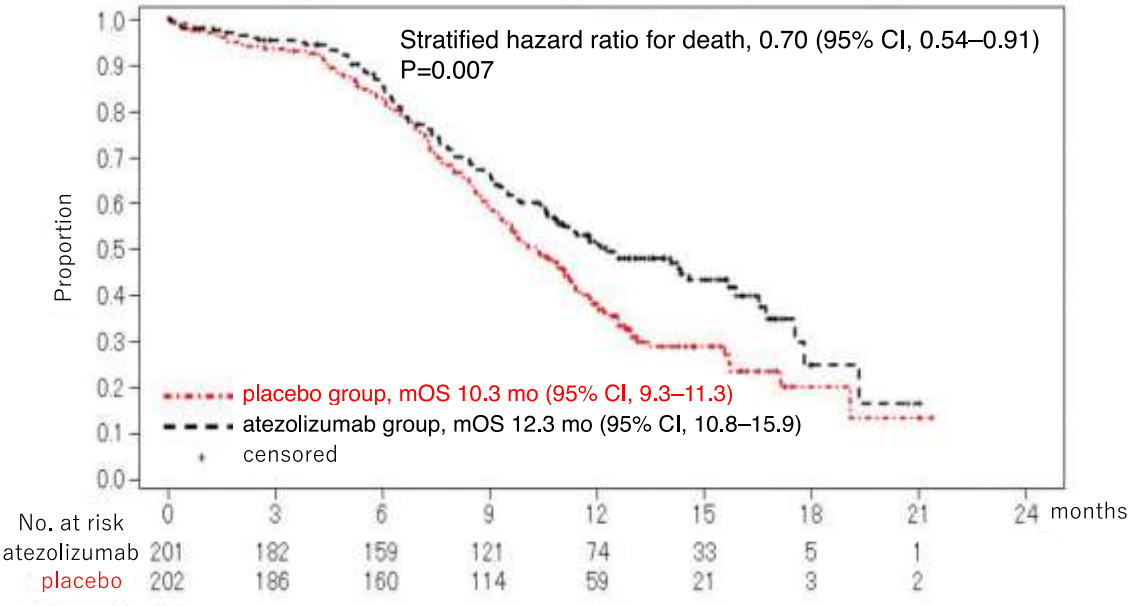
Cisplatin and etoposide have been considered the standard treatment for a long time. Japan Clinical Oncology Group (JCOG) conducted JCOG 9511[3)] to verify first-line combination chemotherapy. ED-SCLC Patients with performance status (PS) under 70 years old were randomized to cisplatin plus irinotecan (PI; cisplatin (60mg/m^2) day 1, irinotecan (60mg/m^2) days 1, 8, 15, every 4 weeks, 4 cycles) or cisplatin plus etoposide (PE; cisplatin (80mg/m^2) day 1, etoposide (100mg/m^2) days 1-3, every 3 weeks, 4 cycles). This trial stopped early because interim analysis demonstrated predefined superiority of PI. The median overall survival (OS) of PI group was 12.8 months compared to 9.4 months in PE group (p=0.002). The median progression-free survival (PFS) was 6.9 months in the PI group and 4.8 months in the PE group (p=0.003). In the study of JCOG 9511, PI was significantly better than PE. Southwest Oncology Group (SWOG) conducted a confirmatory trial using same dose and schedule in both PI and PE (SWOG S0124) [4)]. The median OS of PI group was 9.9 months compared to 9.1 months in PE group (p=0.71). The median PFS was 5.7 months in PI group compared to 5.2 months in PE group (p=0.07). This trial failed to confirm the results of JCOG 9511. Two similar clinical trials were additionally performed comparing PI with PE [5)6)]. Although these 2 trials also failed to confirm the superiority of PI, 3 meta-analyses of irinotecan or etoposide in ED-SCLC patients demonstrated significant survival advantage of irinotecan over etoposide [7)8)9)]. Based on JCOG 9511 and these results of meta-analyses, PI has been standard of care for ED-SCLC patients with PS 0-2 under 70 years old especially in Japan.

A phase III study (IMpower133) for patients with PS 0-1 SCLC was conducted comparing carboplatin + etoposide + atezolizumab (PD-L1 inhibitor) (CBDCA; AUC5 day1, ETP; 100mg/m^2 days 1-3, atezolizumab 1200mg/body day1, every 3 weeks, 4 cycles) followed by atezolizumab maintenance (combination group) and carboplatin + etoposide + placebo [10)]. The combination group showed a significant prolongation of OS as the primary endpoint, compared to the placebo group (12.3 months vs 10.3 months, HR 0.70, 95% CI: 0.54-0.91, P = 0.007) (Fig 1). There was also a significant extension of PFS, as secondary endpoint (5.2 months vs. 4.3 months, HR 0.77, 95% CI: 0.62-0.96, P =

0.02). CBDCA was used in this study, but the median OS in the combination group (12.3 months) was similar to PI (12.8 months) reported in JCOG 9511. Although it should be noted that immunity-related toxicities such as Grade 3 or higher rash (2% vs 0%) and infusion reaction (2% vs 0.5%) tend to increase in the combination group, there was no increase in Grade 3 or higher toxicity in the combination group (56.6% vs 56.1%), including pneumonitis (0.5% vs 1%). An integrated analysis comparing the effectiveness of chemotherapy including cisplatin or carboplatin for SCLC patients, there is no clear difference in effectiveness [11]. Carboplatin + etoposide + atezolizumab administration is considered to be one of the treatment options. Clinical trial results comparing the efficacy and safety of carboplatin + etoposide + atezolizumab and PI were not performed, therefore we need to choose these regimens carefully at the time.

Fig.1 OS of IMpower 133

OS was significantly prolonged in the CE + atezolizumab group



LD-SCLC

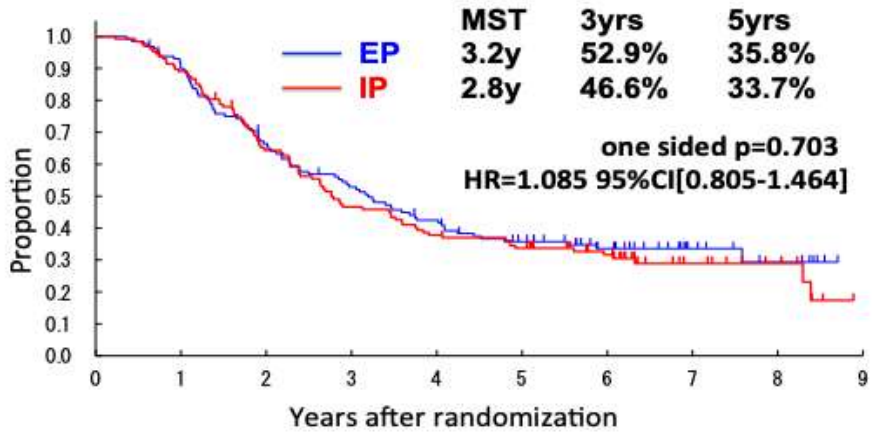
Standard treatment for LD-SCLC patients is regarded as PE with early concurrent chemoradiotherapy (CRT) by accelerated hyper-fractionated thoracic radiotherapy (AHTRT) [12][13][14]. The 5-year survival in PE and twice daily thoracic radiotherapy conducted as the US intergroup study was 26% [15]. JCOG conducted a randomized trial comparing sequential and concurrent PE in combination with twice-daily radiotherapy (JCOG 9104) [16]. 5-year survival of concurrent CRT was 24%, which is similar to the result of intergroup trial in the US.

PI significantly improved OS compared to PE for ED-SCLC as mentioned above. A

randomized phase III trial was performed (JCOG0202) for comparing OS of patients with LD-SCLC [17]. Eligible patients (previously untreated LD-SCLC, age 20-70 years and Eastern Cooperative Oncology Group (ECOG) performance status of 0-1) received one course of PE (etoposide 100 mg/m^2 on days 1-3; cisplatin 80 mg/m^2 on day 1) and concurrent AHTRT (1.5 Gy twice daily, 5 days a week, total 45 Gy, over 3 weeks). After induction CRT, eligible patients were then randomized (1:1 ratio) to standard three courses of continuous PE or PI (irinotecan 60 mg/m^2 on days 1, 8, 15; cisplatin 60 mg/m^2 on day 1). Primary endpoint was OS from randomization after CRT. 281 patients were enrolled and 258 patients were randomized to consolidation PE (n=129) or PI (n=129). Median OS of all patients entered onto the study was 2.9 years, with 3-year survival of 48% and 5-year survival of 34%. Median OS was 3.2 years (95% CI 2.4-4.1) in the PE group and 2.8 years (95% CI 2.4-3.6) in the PI group, respectively. The OS from randomization did not differ between the two groups (hazard ratio 1.09 (95% CI 0.80-1.46), one-sided stratified log-rank p=0.70) (Fig. 2). PFS was also similar between the two groups. The most common grade 3-4 adverse events in PE vs PI were neutropenia (95% vs 78%), anemia (35% vs 39%), thrombocytopenia (21% vs 5%), febrile neutropenia (17% vs 14%), and diarrhea (2% vs 10%). Because the superiority of PI shown in ED-SCLC could not be demonstrated in patients with LD-SCLC, it was concluded that four cycles of PE with AHTRT should continue to be the standard of care for LD-SCLC.

Fig. 2 OS after randomization of JCOG 0202

OS after randomization as primary endpoint was not significantly different between the EP and IP group.



New therapies including immune checkpoint inhibitor

In spite of successful targeted therapy using EGFR-TKIs or ALK-TKIs in Non-SCLC patients, no driver oncogenes have been identified in SCLC so far. The discovery of new driver gene targets needs the elucidation of cell signaling transduction in SCLC.

Table 1 Ongoing clinical studies including immunotherapy

Trial	Phase	Stage	Arm	Primary endpoint
CASPIAN	3	ED	・PE+D+T→D ・PE+D→D ・PE→observation	OS and PFS
KEYNOTE-604	3	ED	・PE+Pem→Pem ・PE+placebo	PFS and OS
NRG-LU005	2/3	LD	・CRT→Atezo ・CRT→observation	PFS (phase2) OS (phase3)
ADRIATIC	3	LD	・D+placebo→D ・D+T→D ・Placebo→Placebo	PFS and OS

Abbreviation
ED; extended disease, LD; limited disease, PE; cisplatin+etoposide, Durv; durvalumab, T; tremelilumab, Pem; pembrolizumab, CRT; chemoradiation

Table 2 State of the art in SCLC from 1983 to 2019

The state of the art in SCLC is progressing by new therapy method and agents.

	LD		ED	
Years	1983	2019	1983	2019
Median Survival (mo)	14	24	7	12-13
3-year Survival (%)	15-20	30-35	0	5-10
5-year Survival (%)	NE	25-30	NE	0-5

Several study using Anti-PD-1 / PD-L1 antibody were conducted a for advanced SCLC with anti-CTLA4 antibody or platinum therapy to expand indications for SCLC (shown in Table 1). Although phase III randomized trial of ipilimumab plus EP vs placebo + EP in ED-SCLC was performed [18], Additional ipilimumab to EP did not prolong OS. In a phase III CASPIAN trial [19], median OS was 13.0 months for the 268 patients who were randomly assigned to receive durvalumab 1500 mg with etoposide plus platinum every 3 weeks for four cycles following maintenance durvalumab every 3 weeks, and was 10.3 months for their 269 patients who received up to six cycles of etoposide plus platinum alone.

At the 12 months, the OS rates were 53.7% and 39.8% for the durvalumab and control arms, respectively. Combination of durvalumab with platinum plus etoposide is an important new treatment option for ED-SCLC patients. At the 12-month mark, the OS rates were 53.7% and 39.8% for the durvalumab and control arms, respectively, while the corresponding rates at 18 months were 33.9% and 24.7%. A Phase 3 randomized, double-blind, placebo-controlled trial of pembrolizumab in combination with etoposide/platinum (cisplatin or carboplatin) for the first-line treatment of patients with ED-SCLC (KEYNOTE-604) is ongoing with estimated primary completion Date (16 December, 2019). NRG-LU005 study is a phase 2/3 study for LD-SCLC patients comparing chemoradiation plus atezolizumab followed by 1-year atezolizumab and chemoradiation followed by observation. A phase III ADRIATIC study for LD-SCLC is comparing 3 regimens after chemoradiation (durvalumab plus placebo 4 cycles followed by 2-year-durvalumab, durvalumab plus tremelimumab 4cycels followed by 2-year-durvalumab, and placebo 4 cycles followed by placebo).

Conclusion

The state of the art of ED-SCLC in 2019 would be 12-13 months median survival and 5-10% as 3-year survival. LD-SCLC in 2019 would be 24 months of median OS, 30-35% of 3-year survival and 25-30% as 5-year survival (table 1). These results are similar to our 2017 manuscript. By many new agents and advanced supportive care for cancer patients, the progress is ongoing slowly but steadily. Patient outcome includes survival and quality of life (21). It is necessary that the choice of treatment should be determined based on effective communication with patients. We need more efforts to improve patients' prognosis and QOL continuously.

Disclosure of Potential Conflicts of Interest]

No potential conflicts of interest were disclosed by Shinji Nakamichi.

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