Editorial

Can combination chemotherapy be standard therapy for sensitive relapsed small-cell-lung cancer?

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Small-cell-lung cancer (SCLC) is a histological type of lung cancer with distinct clinical phenotypes, such as higher response and relapse rates due to rapid acquisition of resistance to chemotherapy. Therefore, second-line treatment is critical for improving survival in SCLC and is delivered with different regimens after the patients are classified into either sensitive or refractory relapse with a cutoff of 2 or 3 months after the first-line treatment. Topotecan monotherapy (1.5 mg/m^2 on days 1 to 5 every 3 weeks) has been a standard of care for sensitive relapse SCLC. Overall survival in relapsed SCLC with topotecan monotherapy was reported to range from 6.2 to 8.7 months in previously conducted phase III trials (1-3).

More recently, Goto and colleagues conducted a randomized phase III trial for sensitive relapse SCLC where combination chemotherapy with cisplatin, etoposide, and irinotecan was compared to topotecan monotherapy as a control arm (4). The combination chemotherapy provided significant survival benefit compared to the topotecan monotherapy. Overall survival for the combination chemotherapy was significantly extended to 18.2 months, whereas patients in the topotecan monotherapy survived for 12.5 months after randomization. About 6-month extension of overall survival was supported by longer progression-free survival (PFS) and higher response rate (RR) in the combination chemotherapy compared to the topotecan monotherapy (5.7 *vs.* 3.6 months for PFS; 84% *vs.* 27% for RR, respectively).

This is the first study to demonstrate the survival benefit of combination chemotherapy in sensitive relapsed SCLC. However, there are problems in this study that can make its clinical application difficult. For instance, there are some imbalances in the prognostic variables between two groups. Patients with 0 of ECOG performance status were more commonly distributed to the combination chemotherapy (58% for the combination chemotherapy *vs.* 44% for the topotecan monotherapy). Median value of days from the first-line chemotherapy to relapse or progression in the combination chemotherapy was 181 days, which was longer than 148 days in the topotecan monotherapy. Such imbalance of prognostic factors may have an impact on survival of the patients. Most importantly, 32% of patients in the combination chemotherapy dropped out due to adverse events and their related refusals while approximately 9% of patients dropped out in the topotecan monotherapy. Grade 3 or more neutropenia and febrile neutropenia were noted in 84% and 31% of the patients respectively despite the preventive administration of G-CSF to all patients in the combination chemotherapy. Presence of concern regarding toxicity remains a significant obstacle in the application of combination chemotherapy to real-world clinical practice. Adding to this issue is a bigger proportion of patients having favorable prognosis in this study, which is not reflective of clinical reality.

In addition, patients in the topotecan monotherapy group received a low dose of 1.0 mg/m^2 but showed longer overall survival compared to the patients who received an approved

dose of 1.5 mg/m^2 of topotecan in previous phase III trials (1-3). Such difference in dosage makes it difficult to form a direct comparison with previous results and to estimate how much relapsed SCLC treatment has progressed based on this study.

Second-line treatment is still a challenge in SCLC. However, more recent clinical application of high throughput technology can facilitate the identification of druggable mutations and selection of patients fit for biological agents (5,6). Several immunotherapeutic agents are being investigated in ongoing clinical trials (7,8). These are expected to provide a new place for relapsed SCLC patients in the near future

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