Editorial

Efficacy of second-line chemotherapy after immunotherapy in advanced non-small cell lung cancer

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Immunotherapy has renewed the standard of care for patients with advanced/metastatic non-small-cell lung cancer (NSCLC) in recent years. Immune checkpoint inhibitors (ICIs) were initially introduced as a monotherapy in second-line or later treatment. Several phase III trials (1-5) of ICI as second-line treatment in patients who previously received platinum-doublet chemotherapy demonstrated that anti-programmed death receptor-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitor monotherapy prolonged overall survival (OS) to a significantly greater degree than docetaxel monotherapy. Subsequently, randomized phase 3 trials (6-10) demonstrated that multiple, ICI-containing regimens were superior to chemotherapy in the first-line setting. Anti-PD-1/PD-L1 antibody monotherapy, multiple anti-PD-1/PD-L1 antibody-containing regimens in combination with platinum-doublet (chemotherapy + anti-PD-1/PD-L1), anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) antibody (anti-PD-1 + anti-CTLA-4) or both (chemotherapy + anti-PD-1 + anti-CTLA-4) are now available as first-line treatments. Thus, most patients with NSCLC tend to receive ICI earlier in their clinical course.

Previous studies suggested an important interaction between cytotoxic chemotherapy and immunotherapy. Immunotherapy sensitizes tumors to chemotherapy by priming the immune system, enhancing its reaction to chemotherapy-induced antigen release (11). In addition, chemotherapy can promote such responses by increasing the immunogenicity of malignant cells or by inhibiting immunosuppressive circuitries that are established by developing tumors (12). ICIs have been combined successfully with chemotherapy as a first-line treatment, and the synergy of both therapies is clinically well established (13). However, the impact of first-line, ICI-based treatment on second-line chemotherapy and the relationship between treatment sequencing patterns and clinical outcomes remain unclear.

Liu *et al.* (14) performed a retrospective cohort study of 13,340 patients with lung cancer in the Mount Sinai Health System. The final study cohort included 2,106 patients with NSCLC who received at least one line of systemic therapy. The study examined the evolution of treatment sequencing as well as the impact of sequencing patterns on clinical outcomes while focusing on the effectiveness of second-line chemotherapy after progression to ICI-based therapy as the first-line treatment. Their study reported a significant shift to more frequent use of ICI-based therapy and multiple lines of targeted therapy after 2015. The clinical

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outcomes of a patient population receiving chemotherapy as the first-line treatment followed by ICI-based therapy (Group 1) and a second patient group receiving a first-line, ICI-containing regimen followed by second-line chemotherapy (Group 2) did not differ significantly in terms of OS [Group 2 *vs.* Group 1; hazard ratio (HR): 1.36; P=0.39]. The study's comparison of the efficacy of second-line chemotherapy in three patient populations receiving their first-line therapy in the form of ICI monotherapy, an ICI-chemotherapy combination, or chemotherapy alone also found no statistically significant difference in terms of time-to-next treatment or OS among the groups. Based on these findings, the authors concluded that two treatment sequencing patterns, namely, ICI followed by chemotherapy or chemotherapy followed by ICI, achieved a similar clinical benefit and that the chemotherapy regimens routinely administered after first-line platinum doublet therapy were effective as a second-line option after the ICI-chemotherapy combination.

Liu *et al.*'s study found that second-line chemotherapy for NSCLC was effective in the post-ICI setting. There are few, previous studies of second-line chemotherapy after first-line, ICI-based treatment. One such study by Heraudet *et al.* (15) demonstrated the impact of prior immunotherapy on chemotherapy efficacy against advanced NSCLC. Their study retrospectively compared 152 patients with advanced NSCLC between 2015 and 2019 who received salvage chemotherapy immediately after ICI administration (CAI group) with ICI-naive patients (CWPI group) who received the same chemotherapy regimen. The study found no difference in the treatment discontinuation rate, OS or overall response rate (ORR) regardless of the chemotherapy regimen but observed a trend toward increased OS when paclitaxel/bevacizumab was administered after ICI. Similar results were reported by Kato *et al.* in the largest cohort to date of Japanese patients, where the ORR for CAI was 18% compared to 11% for CWPI, and no difference in progression-free survival (PFS) or OS was observed (16). These results suggested that some chemotherapy regimens are more effective after immunotherapy. However, there is still a significant lack of data on the efficacy of chemotherapy after immunotherapy. Studies with a NSCLC comparator arm, for instance, would be desirable.

Compared to these previous reports, the study by Liu *et al.* has the advantage of having a large sample pool. However, their study still has some limitations; it was retrospective, and the size of the CAI group was too small for a reliable analysis of second-line chemotherapy. Moreover, chemotherapy regimens without ICI are now rarely used as first-line treatment. Therefore, discussion about the impact of treatment sequences on clinical outcomes differs from actual clinical practice, and their practical use is limited. While second-line treatment options, including docetaxel (with or without ramucirumab), pemetrexed, and gemcitabine, are recommended in clinical guidelines, the pivotal trials demonstrating their activity were conducted before the ICI era, when platinum-based regimens were the standard first-line treatment. It is clinically important to confirm the therapeutic efficacy and re-evaluate the risk-benefit balance of second-line treatments as first-line therapies improve. The results of this study suggested that post-ICI chemotherapy as second-line therapy conferred some survival benefits. However, we must also consider the possibility that some patients will not attain second-line treatment owing to the adverse events related to ICI administration. Today, most patients receive immunotherapy earlier in their clinical course. Therefore, it is important to investigate the effect of first-line ICI-based treatment on second and later lines of treatment. Further studies are warranted to determine whether ICI improves the efficacy of subsequent chemotherapy.

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