Letter to the Editor

The need to optimize chemotherapy regimens for chemo-immunotherapy

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The phase 3 CheckMate 816 trial demonstrated that neoadjuvant nivolumab-plus-chemotherapy treatment significantly improved event-free survival compared to neoadjuvant chemotherapy-alone treatment [hazard ratio (HR) for disease progression, disease recurrence, or death, 0.63; 97.38% confidence interval (CI): 0.43–0.91; P=0.005] in patients with IB–IIIA resectable non-small cell lung cancer (NSCLC) (1). The pathological complete response (pCR) rate was 24.0% in the nivolumab-plus-chemotherapy group and 2.2% in the chemotherapy-alone group (odds ratio, 13.94; 99% CI: 3.49–55.75; P<0.001) (1). Based on these results, the U.S. Food and Drug Administration approved nivolumab with platinum-doublet chemotherapy for adult patients with resectable NSCLC in neoadjuvant setting on March 4th, 2022 (2).

Chemo-immunotherapy has emerged as a promising strategy for cancer treatment. Cytotoxic chemotherapy not only kills tumor cells but also augments antitumor immunity by exposing tumor antigens and inducing immunogenic conditions. This antigen-induced effect can result in a dramatic synergy with immunotherapy, which potentially leads to pCR (1). Thus, in chemo-immunotherapy, the essential role of chemotherapy would be antitumor immunoboosting rather than tumor-cell killing. In this situation, metronomic (low-dose frequent administration) chemotherapy has proven to be effective in priming tumors for immunotherapy (3). Nonetheless, most chemo-immunotherapy trials, including the CheckMate 816 trial (1), administer standard full-dose cytotoxic chemotherapy.

We have two concerns about the CheckMate 816 trial (1). First, the discontinuation rate was lower in the nivolumab-plus-chemotherapy group (6.2%) than in the chemotherapy-alone group (15.3%) (1), although most combination therapies, including chemo-immunotherapy (e.g., the KEYNOTE 189 trial) (4), increase discontinuations. Survival benefits were higher in patients receiving less-toxic and more-tolerable carboplatin (HR, 0.31; 95% CI: 0.14–0.67) than in patients receiving cisplatin (HR, 0.71; 95% CI: 0.49–1.03). We speculate that side effects may have caused differences in chemotherapy dose density and intensity between the nivolumab-plus-chemotherapy group and the chemotherapy-alone group. Preferable-interval chemotherapy might contribute to the efficacy of nivolumab-plus-chemotherapy treatment, although the provided data is insufficient to test these hypotheses. Detailed information would help optimize chemotherapy dose density and intensity in neoadjuvant chemo-immunotherapy. Second, survival benefits were higher in patients with pretreatment tumor PD-L1 expression ≥50% (HR, 0.24; 95% CI: 0.10–0.61) than in patients with PD-L1 expression <1% (HR, 0.85; 95% CI: 0.54–1.32) (1). Preclinical and clinical evidence demonstrates that cytotoxic chemotherapy can increase tumor PD-L1 expression (5), sensitizing tumors to nivolumab. Therefore, certain chemotherapeutic agents might particularly enhance the response to nivolumab by increasing tumor PD-L1

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expression. We wonder whether chemotherapy increased tumor PD-L1 expression, and if so, whether the transformed tumors responded to nivolumab, and which regimens had this effect. Such information would be valuable in strategizing not only neoadjuvant but also adjuvant and palliative chemo-immunotherapy.

In an emerging era of integrative chemo-immunotherapy, we should not merely apply standard chemotherapy regimens. In order to maximize the efficacy of chemo-immunotherapy, much effort should be made to determine the best treatment regimen for chemotherapy-immunotherapy combinations.

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