PD-L1 ≥ 50% lung cancer refractory to PD-1 inhibition: The role of salvage chemo-immunotherapy combination

When PD-L1 ≥ 50% is not enough: The role of salvage chemo-immunotherapy combination for pembrolizumab-refractory NSCLC.

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First-line treatment approaches in advanced non-small cell lung cancer (NSCLC) have dramatically evolved in the last few years.[1] Here we report the differential outcomes of three adenocarcinoma lung cancer patients, with PD-L1 tumor proportion score (TPS) ≥ 50%, who rapidly progressed on pembrolizumab monotherapy and were then switched to carboplatin-pemetrexed-pembrolizumab combination. All patients harbored activating *KRAS* mutations affecting codon 12, started pembrolizumab (200 mg every three weeks) in good clinical conditions (ECOG PS 0), had not received antibiotics in the month before and were not undergoing baseline steroid treatment. All patients become symptomatic during pembrolizumab monotherapy (ECOG PS 1).

Patient #1 (40-year-old, light smoker) presented with lung, pleural, nodal, bone and brain metastases; PD-L1 TPS was 90%. Only one pembrolizumab course was administered, as supra- and infra-diaphragmatic (massive left pleural effusion and peritoneal carcinomatosis, Figure 1) developed. After pleural effusion drainage with pleurodesis, carboplatin (AUC 5) + pemetrexed (500 mg/mq) + pembrolizumab was introduced, leading to impressive response (Fig. 1), maintained three months after combination treatment start.

Patient #2 (58-year-old, current smoker) had undergone drainage of malignant pericardial tamponade before starting pembrolizumab (PD-L1 TPS 80%). He had lung, pleural, pericardial, nodal (thoracic, abdominal) and bone disease. Pericardial effusion worsening after two pembrolizumab cycles required multiple drainage before chemotherapy-pembrolizumab combination start, leading to systemic response maintained after four cycles of induction and four of pemetrexed-pembrolizumab maintenance (doses reported above).

Patient #3 (64-year-old, former smoker) presented with lung, pleural, hepatic and bone disease. A *TP53* R273L mutation was detected in addition to the *KRAS* G12C one. PD-L1 TPS was 70%. All disease sites progressed after five pembrolizumab cycles. Symptomatic bone progression and the appearance of choroidal metastases required palliative radiotherapy. Switching to the combination of chemotherapy-pembrolizumab (two cycles, doses reported above) did not change disease course, as he passed away before further radiologic assessment.

No peculiar toxicities emerged in any of the three cases, both during pembrolizumab and chemotherapy-pembrolizumab.

Albeit all in good clinical conditions before treatment start (ECOG PS = 0), the three patients had high disease burden with multiple (≥ three) disease sites:[2] nodal, pleural and bone metastases were present in the all the cases, as well as serosal progression to pembrolizumab (pleural, peritoneal, pericardial).[3] No additional prognostic factors suggesting worst clinical outcomes were noticed (antibiotics, steroids received before pembrolizumab). It can be argued that in patients #1 and #2, chemotherapy alone would have been as beneficial as the combination with pembrolizumab, and that in patient #3 even the combination regimen as treatment of choice would not have been able to counteract disease aggressiveness. Nevertheless, as reported by another report, evoking the immunomodulatory effect of chemotherapy,[4] the present one vouches for the feasibility and potential activity of salvage chemotherapy-pembrolizumab for NSCLC refractory to pembrolizumab monotherapy.

To date, clinical-biological factors supporting clinicians' decisions for patients suffering from newly diagnosed metastatic NSCLC with PD-L1 TPS ≥ 50% are lacking. Taking into account that *KRAS* mutations are not deemed to affect immunotherapy action,[5] the presence of a high tumor burden including serosal disease,[2,3] as reported in our small series, could be responsible for the refractoriness to pembrolizumab monotherapy. These observations suggest the use of chemo-immunotherapy combination as the up-front treatment in this subgroup of patients, even if in good clinical conditions.

Figure legend

Figure 1. CT-scans of patient #1. The massive pleuro-peritoneal progression and the dimensional increase of lung lesions observed after one pembrolizumab cycle (central column) were almost completely regressed after three carboplatin-pemetrexed-pembrolizumab courses (right column).

References

1. Ackermann CJ, Reck M, Paz-Ares L, Barlesi F, Califano R. First-line immune checkpoint blockade for advanced non-small-cell lung cancer: Travelling at the speed of light. *Lung Cancer*. 2019;134:245-253.
2. Tambo Y, Sone T, Shibata K, et al. Real-world efficacy of first-line pembrolizumab in patients with advanced or recurrent non-small cell lung cancer and high PD-L1 tumor expression. *Clin Lung Cancer*. 2020 February 25 [Epub ahead of print].

3. Kawachi H, Tamiya M, Tamiya A, et al. Association between metastatic sites and first-line pembrolizumab treatment outcome for advanced non-small cell lung cancer with high PD-L1 expression: A retrospective multicenter cohort study. *Invest New Drugs*. 2019;38:211-218.
4. Garcia CA, Dacic S, Villaruz LC. Disease response with the addition of platinum-based chemotherapy to pembrolizumab after progression on pembrolizumab monotherapy in PD-L1-expressing non-small cell lung cancer. *J Thorac Oncol*. 2018;13:e135-136.
5. Jeanson A, Tomasini P, Souquet-Bressand M, et al. Efficacy of immune checkpoint inhibitors in *KRAS*-mutant non-small cell lung cancer (NSCLC). *J Thorac Oncol*. 2019;14:1095-1101.