CLINICAL VIGNETTE

PD-L1 Immunotherapy in Non-Small Cell Lung Cancer (NSCLC): The Dilemma of Relative Success

Alexander C. Black, MD

A 72-year-old woman with a history of right thyroidectomy for benign disease in her late 30s and a 70-80 pack year cigarette smoking history which had ended a year earlier who began noticing left facial spasms. Her internist evaluation included labs which showed hypercalcemia, 11.1 mg/dL and a parathyroid hormone level (PTH) of 70 pg/mL, slightly above the upper limit of normal, and a bone density scan which showed osteoporosis. She underwent a CT parathyroid/ thyroid scan which revealed a 1.2 cm possible left parathyroid adenoma and a 4 cm pre-carinal mass. Follow up imaging included a chest CT which confirmed the mediastinal and hilar adenopathy but no lung parenchymal lesions and PET CT showed strongly PET + mediastinal adenopathy up to 3 cm and a 2.1 cm right hilar lymph node and per-pancreatic lymph nodes, consistent with metastatic disease. She underwent a mediastinotomy with biopsy which revealed a poorly differentiated adenocarcinoma with immunohistochemical stains not clearly confirming a tissue of origin.

Her multiple specialists concurred on the clinical diagnosis of metastatic NSCLC. She received chemotherapy with immunotherapy, specifically 6 cycles of 3-week cycles of carboplatin and paclitaxel chemotherapy along with the PD-L1 monoclonal antibody inhibitor pembrolizumab iv once every 3 weeks. Follow up PET CT scan after 3 cycles showed a complete metabolic response which was confirmed after all 6 cycles on repeat PET. Six months later, on pembrolizumab maintenance immunotherapy the patient underwent resection of the enlarged parathyroid gland which revealed hyperplasia but no malignancy. Her hypercalcemia subsequently resolved.

Serial PET scans confirmed a continued metabolic complete remission (CR) and CS was continued on pembrolizumab. Three to four months after her parathyroidectomy she began experiencing musculoskeletal pain, primarily in joints. Her initial testing showed no elevation in inflammatory markers 3 months into her symptoms but by 6 months her erythrocyte sedimentation rate (ESR) was elevated at 44 mm/hr and her C reactive protein (CRP) was elevated at 6.3 and her PET scan, while confirming continued metabolic CR, showed increased metabolic activity in shoulders and hips and wrists consistent with arthritis. She was seen by rheumatology who, after an extensive work up diagnosed polymyalgia rheumatica (PMR) and started prednisone 20 mg daily with a slow taper. Her prednisone was tapered based on her arthralgia complaints which had improved substantially with treatment and with resolution of the joint inflammation described on PET at the time of her PMR diagnosis. Pembrolizumab was continued and the prednisone was tapered to 4 mg daily over 12 months. To date, now over 2 ½ years into pembrolizumab maintenance therapy the patient remains in CR.

Discussion

Targeting the PD-1/ PD-L1 pathway with monoclonal antibodies which block the interaction can effectively reverse an immunosuppressive effect of cancer cells expressing PD-L1 which inhibit activated T cells and antigen presenting cells expressing PD-1.[1] Several monoclonal antibodies target PD-1, like pembrolizumab, while others target PD-L1 with similar clinical effectiveness. Median overall survival in advanced non-small cell lung cancer has increased from 12-14 months with prior optimal therapy to over 24 months and the proportion of patients alive at 5 years is 2-3 fold higher with the addition of immunotherapy.[1,2] It is not clear if immunotherapy might be curative in a small proportion of metastatic NSCLC patients.

Unlike chemotherapy immunotherapy has no dose dependent predictable side effects and many patients have mild to no side effects even on long term therapy. However, there are many potential autoimmune toxicities which can occur at any time during the course of therapy. This patient's PMR clearly responded to prednisone, but developed after one year on pembrolizumab. She was able to receive moderate then tapered to low dose prednisone without a loss of her clinical CR. Hence PMR was likely a pembrolizumab induced complication but was mild and manageable and did not require stopping immunotherapy. In a comprehensive meta-analysis of immunotherapy toxicity in 23,322 patients from 52 randomized clinical trials, adverse events (AE) due to immunotherapy were reported in 35-40% of patients and serious AE meriting discontinuation of immunotherapy in 4%, relatively less on single agent PD L1 inhibitor monotherapy as compared to combined immunotherapy targeting the PD-L1 and CTLA 4 pathways.[3]

Patients who have maintained cancer control, from stable disease to CR, the optimal duration of immunotherapy remains unclear. Most studies have compared added immunotherapy to chemotherapy only with durations of treatment of one year or 2 years or indefinite. In an exploratory analysis, lung cancer

investigators in a chemotherapy with or without nivolumab, a PD-1 inhibitor similar to pembrolizumab, study added a second randomization of patients to either one-year fixed duration or continuous nivolumab after one year of cancer control.[4] Of 1428 study patients, 252 were randomized at one year with 127 on the continuation arm and 125 on the cessation of immunotherapy arm. Estimated median overall survival was 32.5 months in the one-year arm and not reached in the continuation arm, suggesting a survival benefit of sustained maintenance immunotherapy.[4]

Assessing the cost effectiveness of immunotherapy is challenging and ideally should incorporate efficacy, cost and adverse events. In a review of peer reviewed and published cost effectiveness analyses of pembrolizumab in advanced lung cancer, there were many different modeling and cost estimation approaches.[5] Overall the Institute for Clinical and Economic Review, an independent agency performing cost effectiveness reviews, estimated a $ 100-120, 000 per quality adjusted life year cost for pembrolizumab in lung cancer.[5] The acceptable cost for positive clinical outcomes, particularly in the subset of long-term survivors, remains a matter for research and national debate.

REFERENCES

1. **Shields MD, Marin-Acevedo JA, Pellini B**. Immunotherapy for Advanced Non-Small Cell Lung Cancer: A Decade of Progress. *Am Soc Clin Oncol Educ Book*. 2021 Mar;41:1-23. doi: 10.1200/EDBK_321483. PMID: 33979196.
2. **Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC, Garassino MC; KEYNOTE-189 Investigators**. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018 May 31;378(22):2078-2092. doi: 10.1056/NEJMoa1801005. Epub 2018 Apr 16. PMID: 29658856.
3. **Zhou C, Li M, Wang Z, An D, Li B**. Adverse events of immunotherapy in non-small cell lung cancer: A systematic review and network meta-analysis. *Int Immunopharmacol*. 2022 Jan;102:108353. doi: 10.1016/j.intimp.2021.108353. Epub 2021 Dec 6. PMID: 34883352.
4. **Waterhouse DM, Garon EB, Chandler J, McCleod M, Hussein M, Jotte R, Horn L, Daniel DB, Keogh G, Creelan B, Einhorn LH, Baker J, Kasbari S, Nikolinakos P, Babu S, Couture F, Leighl NB, Reynolds C, Blumenschein G Jr, Gunuganti V, Li A, Aanur N, Spigel DR**. Continuous Versus 1-Year Fixed-Duration Nivolumab in Previously Treated Advanced Non-Small-Cell Lung Cancer: CheckMate 153. *J Clin Oncol*. 2020 Nov 20;38(33):3863-3873. doi: 10.1200/JCO.20.00131. Epub 2020 Sep 10. PMID: 32910710; PMCID: PMC7676888.
5. **Qiao N, Insinga R, de Lima Lopes Junior G, Cook J, Sénécal M**. A Review of Cost-Effectiveness Studies of Pembrolizumab Regimens for the Treatment of Advanced Non-small Cell Lung Cancer. *Pharmacoecon Open*. 2021 Sep;5(3):365-383. doi: 10.1007/s41669-020-00255-2. Epub 2021 Jan 19. PMID: 33469803; PMCID: PMC8333166.