Immunotherapy Resistance in Non-Small Cell Lung Cancer

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Received 20 September 2021; **Accepted** 25 September 2021; **Published** 30 September 2021

Editorial

Lung cancer is the leading cause of cancer-related death and the second most common malignancy reported in the United States and around the world. It is expected that in 2020, there will be 228,820 new cases of lung cancer and 135,720 deaths from lung cancer. The total number of deaths caused by lung cancer exceeds the total number of deaths caused by colon, prostate, and breast cancer combined. This poor outcome in lung cancers is due, in part, to the fact that more than half of the patients, or approximately 55%, had metastatic lung cancer at the time of diagnosis. Finally, non-small cell lung cancer (NSCLC) accounted for approximately 85 percent of newly diagnosed lung cancer cases. Patients with advanced NSCLC have metastatic disease or recur after receiving initial definitive treatment. With only supportive care, the median overall survival (OS) for patients with metastatic NSCLC is about 4-5 months. Historically, the median OS for patients who received supportive care in addition to induction platinum-based chemotherapy was 8-12 months. Multiple trials comparing different chemotherapy regimens have resulted in marginal improvements in OS for decades. The study of the therapeutic benefits of chemotherapy has reached a halt. The results of a randomised phase III trial comparing four platinum-based doublets in first-line metastatic NSCLC were published in 2002 by the Eastern Cooperative Oncology Group. The trial found no difference in overall survival between the various treatment regimens.

The discovery of particular driver mutations and the creation of targeted therapy were key breakthroughs in the treatment of metastatic NSCLC. Despite the small number of patients having actionable mutations, patients treated with targeted therapy had a considerably higher progression-free survival rate than those treated with chemotherapy. Patients with EGFR, ALK, ROS1, and BRAF mutations who underwent targeted therapy had a response rate of 50 to 80 percent. The average length of survival was raised to 18 to 38.6 months. Immunotherapy (IO) and, in particular, immune checkpoint inhibitors (ICI), such as programmed death receptor 1 (PD-1) and PD-ligand 1 (PD-L1) inhibitors, have changed the way non-small cell lung cancer is treated (NSCLC). Long-term responses in advanced stage disease were previously unanticipated, with a 5-year overall survival (OS) of 20% in unselected patients and up to 40% in PD-L1high expressing patients.

Despite the dramatic clinical improvements, the majority of patients eventually fail to react to ICI therapy as main or secondary resistance develops. Prospective clinical studies to show treatment methods after IO therapy progression are still missing. Various IO resistance mechanisms have been identified, including innate and environmental resistance patterns in tumour cells. The tumour microenvironment (TME) is important because it affects both extrinsic and intrinsic resistance mechanisms. A deeper knowledge of the heterogeneous TME will pave the way for further optimization of tactics and new directions in IO therapy stratification in the future.

There are a slew of new preclinical and clinical therapy options aimed at overcoming IO resistance in NSCLC patients. The intricacy of cellular and molecular changes inside the immunosuppressive TME provides the foundation for developing rational and synergistic combination therapies that reduce the likelihood of resistance while extending the duration of IO therapy efficacy.

Cite this article: Shikha S. Immunotherapy Resistance in Non-Small Cell Lung Cancer. Oncol Cancer Case Rep. 2021, 07(9), 001-001.