

Immunotherapy for lung cancer: Its time has finally come

There has never been such an exciting time to be an oncologist and investigator in lung cancer. Even as recently as the early 2000s, systemic therapy for lung cancer still relied on combinations of cisplatin-based chemotherapy, which were associated with moderate or severe toxicity in up to 50% of cases and dismal 5-year overall survival rates of only about 1% to 5% for patients with stage IV disease. Over the past decade, image-guided radiotherapy, particularly intensity-modulated radiotherapy (IMRT) and stereotactic ablative radiotherapy (SABR), has fundamentally improved the ability to precisely target tumors even in complex anatomic locations, which has led to reduced toxicity, increased local/regional control, and even improved survival for patients with early-stage or locally advanced lung cancer. However, distant metastasis remains the dominant pattern of failure after definitive local therapy. In addition, even now most patients are found to have stage IV disease when the lung cancer is diagnosed. Over a similar period, the advent of personalized molecular targeted therapy has significantly improved rates of response and overall survival in the roughly 20% to 30% of patients with metastatic lung cancer that harbors mutations in the genes for EGFR, ALK, ROS-1, and BRAF. But what about the rest of the patients, those without targetable gene mutations?

Immunotherapy was not considered an option for lung cancer treatment until about 2015, when PD-1 checkpoint immunotherapy was found to improve progression-free survival and, later on, overall survival rates (up to 16% at 5 years) with fewer and much less severe side effects than second-line chemotherapy for patients with stage IV non-small cell lung cancer (NSCLC) that did not respond to conventional first line chemotherapy. Amazingly, in a very brief time immunotherapy has moved from second-line to first-line therapy for stage IV squamous or non-squamous cell lung carcinoma, being given as PD-1 immunotherapy alone, or in combination with CTLA4 immunotherapy, or in combination with conventional chemotherapy or angiogenesis inhibitors depending on the tumor's PD-L1 status, total mutation burden, and the presence of other molecular markers. After the June 2018 meeting of the American Society of Clinical Oncology, conventional chemotherapy is being edged over to second-line therapy, or as an adjunct to immunotherapy, for many patients with lung cancer. Indeed, the US National Comprehensive Cancer Network modified its guidelines several times in 2017 and again in 2018 based on the emerging scientific evidence in support of immunotherapy.

By the end of 2017, adjuvant PD-L1 immunotherapy was found to improve progression-free survival for patients with stage III NSCLC treated with concurrent chemo-radiotherapy, and subsequently a benefit in terms of overall survival was reported as well. This is the first time in the past decade that overall survival has significantly improved for patients with stage III NSCLC, as demonstrated in a prospective randomized study that included radiotherapy as definitive local therapy. Indeed, in various combinations with radiotherapy, surgery, and chemotherapy, immunotherapy has shown promising early results for both early and locally advanced lung cancer.

However, at this time the response rates of unselected patients with lung cancer to PD-1/PD-L1 immunotherapy alone remain low at 20% to 30%, underscoring the ongoing need to optimize immunotherapy for individual patients based on novel molecular markers. Moreover, combining immunotherapy with other forms of treatment such as chemotherapy, radiotherapy, or both may well overcome the development of resistance to immunotherapy and improve the therapeutic ratio. This has been a most exciting time for clinical research on this topic. The concept of combining immunotherapy with stereotactic ablative radiotherapy (I-SABR) has triggered extensive interest, and hundreds of preclinical and clinical studies are now ongoing. I-SABR and other strategies for optimizing immuno-radiotherapy are also being proposed in 2018. There is no doubt that tomorrow's lung cancer patients will be better treated than today's. This book provides unique, up-to-date information about the paradigm shift in biology and technology prompted by the advent of immunotherapy. More is coming. Stay tuned.



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