

LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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Moving Beyond Monotherapy in the Immunotherapeutic Arena: Prospects for Combination Therapies in Lung Cancer



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H&O Why would patients with lung cancer benefit from a new treatment modality beyond surgery, chemotherapy, and radiation?

SA Treatment of lung cancer depends on the stage. Patients with early-stage lung cancer, known as stage 1, still have a very good chance of being cured with surgery alone. Chemotherapy and surgery can potentially cure patients with stage 2 disease. Patients with stage 3 disease can be cured by chemotherapy and radiation, with or without surgery. These modalities are still the standard of care and are associated with a good chance of cure.

Unfortunately, most patients with lung cancer present with stage 4 disease, which is advanced or metastatic. In these patients, surgery is not an option. Radiation is used only with palliative intent; it does not improve overall survival. Chemotherapy is still effective in increasing the survival of patients with metastatic disease, but it is not curative. Therefore, we need to develop new treatment modalities for patients with advanced disease, and to improve cure rates for patients with earlier-stage disease.

H&O What types of immunotherapies are being used in lung cancer?

SA Lung cancer is an immunotherapeutically responsive disease, but there are several ways in which lung cancers evade rejection by the immune system. In some patients, the number of tumor-reactive T cells may be insufficient.

In others, tumor-reactive T cells fail to enter the tumor. In some cases, the T cells are functionally shut down when they enter the tumor.

There are various strategies in use to combat these deficiencies. The number of tumor-reactive T cells can be increased with a therapeutic cancer vaccine or adoptive T-cell therapy. With adoptive T-cell therapy, tumor-infiltrating lymphocytes are expanded *ex vivo* or peripheral T cells are redirected by transfecting them with chimeric antigen receptors (CARs) or T-cell receptor genes, where the T-cell receptor is reactive to a tumor-specific antigen. Other strategies focus on the immunosuppressed tumor microenvironment. Immunosuppressive monoclonal antibodies are directed at the immune checkpoints, which are T-cell surface proteins that send a negative signal to the T cells when they bind to their ligands. In development are monoclonal antibodies that bind to these immune checkpoints, thereby preventing them from binding to their ligands and sending a negative signal to the T cell. Monoclonal antibodies directed against the anti-programmed cell death protein 1 (PD-1) are an example.

Clinical trials in lung cancer are currently evaluating monoclonal antibodies against immune checkpoints such as lymphocyte-activation gene 3 (LAG-3), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3). Trials are testing these novel agents in combination with those targeting PD-1. Clinical trials are also evaluating small molecule inhibitors against the immune checkpoint adenosine A2A receptor.

H&O Why is lung cancer responsive to immunotherapy?

SA An important reason is that lung cancer tumor cells have many mutations; only melanoma is associated with a higher number. The more mutations there are, the greater the chance that a mutation will be located in an epitope that is loaded onto the surface of the major histocompatibility complex class (MHC) I molecules and will be perceived as foreign by the immune system.

H&O What are the advantages of immunotherapy over other types of cancer treatments?

SA In randomized trials of patients with lung cancer, immunotherapy appears to produce a significant improvement in median overall survival as compared with chemotherapy, certainly in the second-line setting. What is more interesting, however, is that immunotherapy may have a positive influence on the tail of the survival curve, meaning that in patients who respond to treatment, those responses can be durable. It is still early, but there is hope that there will be long-term survivors, which has not been seen with the other therapeutic modalities.

H&O Which immunotherapeutic agents are now available for lung cancer?

SA There are 2 commercially available immunomodulatory antibodies for lung cancer. Nivolumab (Opdivo, Bristol-Myers Squibb) and pembrolizumab (Keytruda, Merck) are anti-PD-1 antibodies with similar efficacy and safety profiles. In randomized clinical trials, nivolumab and pembrolizumab have produced benefits beyond those expected from the standard-of-care second-line chemotherapy, docetaxel. These agents not only increase median overall survival, but appear to have a positive impact on the tail of the survival curve.

The current indication is to use anti-PD-1 agents as monotherapy in the second-line or greater setting. Combinations will soon be available for certain clinical settings. The first approved combination will be an anti-CTLA-4 agent with either an anti-PD-1 or anti-PD-ligand 1 (PD-L1) antibody.

H&O Are there data suggesting an improved response with combination strategies?

SA The use of combination therapy in different clinical settings is currently under evaluation. An improvement in overall survival is expected, although it is now too early for confirmation. The objective tumor response rates, which are a surrogate for overall survival, are

improved with combinations over monotherapy with either anti-CTLA-4 or anti-PD-1 agents.

There may be a stronger benefit in certain patient subsets. What looks most promising is that combination immunotherapy, for example, with anti-CTLA-4 and anti-PD-1 or anti-PD-L1 therapies, may have more activity in patients whose tumors do not express the PD-L1 biomarker.

H&O Is there synergy between immunotherapy and other treatments, such as chemotherapy and targeted therapy?

SA That is unknown and being tested right now. There is no proven synergy between chemotherapy and immunotherapy, but there may be. It may also be the case that there is not synergy but just the additive effects of different treatment modalities, in which case, sequential therapy may be just as good as concurrent therapy.

There are theoretical reasons why there could be potential synergy with immunotherapy and radiation. The release of tumor antigens in a radiated tumor in an immunogenic fashion could produce more tumor-reactive T cells locally that could recirculate and work in distant metastatic deposits in the presence of anti-PD-1, for example.

H&O What has your research into vaccines for lung cancer shown?

SA We have tested a p53 vaccine in small cell lung cancer and another one in non-small cell lung cancer. There was low clinical activity, as is the case with nearly all other therapeutic tumor vaccines. Prior to the advent of anti-PD-1 therapy, there was pessimism about moving forward with therapeutic tumor vaccines in lung cancer. However, now many in the field have the perspective that the tumor vaccines did what they were supposed to do: they expanded tumor reactive T cells. Both of our vaccines did that. We know now that this expansion is insufficient because once these T cells entered into the tumor microenvironment, they were shut down when exposed to PD-L1. The new immunotherapies have provided a therapeutic tool with which to prevent that from happening. There is hope that the combination of anti-PD-1 or anti-PD-L1 antibodies with tumor vaccines will produce synergy. Like many investigators, we are now retesting our therapeutic tumor vaccines in combination with these new treatments.

H&O Are there any other mechanisms that tumors use to avoid the immune response?

SA There are numerous other mechanisms that tumors

use. For example, in the tumor microenvironment, there can be aberrant expression of several different ligands for different immune checkpoints that combine with LAG-3, TIM-3, CTLA-4, or PD-1. The tumor microenvironments have a high concentration of adenosine, which binds to the immune checkpoints. Adenosine binds to the adenosine A2A receptor on T cells, which is a potent inhibitor of T cells. Immunoinhibitory cytokines include interleukin 10 (IL-10) and tumor growth factor β (TGF- β). There can also be metabolic alterations. Immunosuppressive enzymes, such as indoleamine 2,3-dioxygenase and arginase, are immunosuppressive. Tumors contain a variety of nonmalignant cells that are immunosuppressive, including suppressive regulatory T cells (Tregs). Myeloid cells and cancer-associated fibroblasts can be immunosuppressive in the tumor microenvironment, as well.

H&O What is the potential for immunotherapy in lung cancer?

SA There has been a fairly dramatic impact on the clinical outcomes of patients treated with anti-PD-1 therapy, and that is just with monotherapy targeting a single immunosuppressive mechanism. There is a huge potential for continued overall improvement in clinical outcomes by understanding the proper immunosuppressive blocking agents to be used in individual patients.

The challenge is that tumors can evade rejection in a myriad of ways. Even among patients with the same tumor type, there is considerable heterogeneity in the immunosuppressive mechanisms that are operational.

Therefore, the main challenge is how to understand what combinations in which individual patients are going to be beneficial. The development of proper biomarkers is paramount.

Disclosure

Dr Antonia is an advisor/consultant to BMS, MedImmune, AZ, CBMG, Merck, Genentech, and Palobiofarma.

Suggested Readings

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