LUNG CANCER CANADA

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Harnessing the Immune System:
Progress in the treatment of non-small cell lung cancer

By Dr Peter Ellis

The immune system has been considered a therapeutic target in cancer for several decades now. There have been many studies of vaccine based treatments and other immune based therapies such as interferons and interleukins, but these have been mostly unsuccessful. However, stimulating a person's immune system to fight their cancer remains an appealing treatment strategy. Recent advances in immune-based therapy provide much hope and promise that these approaches to treatment will benefit patients with lung cancer.

New developments in vaccines

Older trials of vaccine based therapy for lung cancer did not improve the treatment for patients with lung cancer. However, a recent trial holds some promise. Tecemotide is a vaccine that targets the Mucin-1 antigen (MUC-1). A large international trial of tecemotide or placebo, in patients with stage III non small cell lung cancer (NSCLC) treated with chemoradiation, was recently published.[1] The trial did not show an improvement in overall survival for patients who received tecemotide after chemoradiation. However, a subgroup analysis of patients who received chemotherapy and radiation concurrently (rather than sequentially), suggested this group benefited from tecemotide. The side effects of tecemotide are generally mild. These results appear promising and in order to confirm these results, a further trial of tecemotide in patients receiving concurrent chemoradiation has been started.

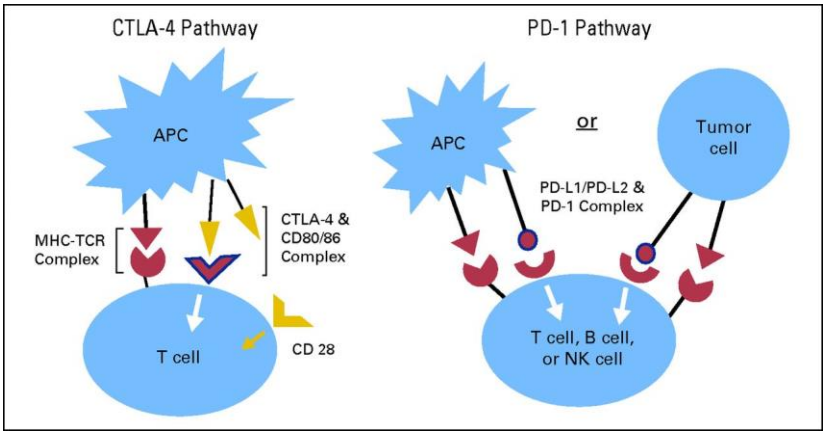

Figure 1 The cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitory checkpoint pathway is important in regulating early T-cell activation.

Modulating the immune system

There is a lot of excitement about drugs that modulate the immune system (called checkpoint inhibition). Regulation of the immune system is complex. Certain white blood cells called T-cells are a central part of this regulation (Figure 1). There are signals that stimulate the immune system and signals that slow down (down regulate) the immune system. Proteins (ligands) such as CD80 and CD86, Cytotoxic T Lymphocyte Antigen 4 receptor (CTLA-4), Programmed cell death – 1 ligand (PD-L1) and its receptor (PD-1) are all important in down regulating the immune responses. This is one way in which cancers can hide from the immune system, by increasing expression (increasing the amount of) CTLA-4 or PD-L1.

Antibody treatments have been developed to block the effect of CTLA-4 or PD-L1 on the immune system. Removing these inhibitory signals (checkpoint inhibition), allows the body's immune system to recognize the cancer and more effectively attack the cancer cells.

Ipilimumab is a monoclonal antibody that blocks CTLA-4 and allows activation of cytotoxic T lymphocytes. Ipilimumab is already approved for the treatment of metastatic melanoma. In patients with metastatic NSCLC, it was tested in combination with chemotherapy. Giving ipilimumab after standard chemotherapy controlled the cancer for a longer time (improved progression free survival) than standard chemotherapy with carboplatin and paclitaxel.[2] Phase III trials are ongoing to determine if this strategy will help patients with NSCLC to live longer. A similar antibody, tremelimumab is also being tested in NSCLC as well as mesothelioma. Activating the immune system has the potential to attack healthy cells in the body (immune related toxicities). These include inflammation in the lungs (pneumonitis), liver (drug induced hepatitis) and endocrine glands such as the thyroid and pituitary, rash, diarrhea, although serious side effects are uncommon.

There are a number of monoclonal antibodies that attack either PD-1 receptor (nivolumab, MK-3475, Medi-4376), or the ligand PD-L1 (MPDL-3280A). As a result, cells in the immune system are switched on and more able to recognize and fight the cancer. A phase I clinical trial of nivolumab in patients with a variety of cancers, who had all received other therapies, showed that nearly one in five patients had significant response to nivolumab. [3] At the 2013 World Congress in Lung Cancer data were presented from early phase clinical trials summarising the activity of nivolumab, MK-3475 and MPDL-3280A. All of these trials included patients with NSCLC who had received two or more previous therapies. Approximately 20% of patients responded to therapy with one of these agents. Many of these patients who responded to treatment remained well a year or more later. Some groups of patients (those with tumors that had higher levels of the PD-L1) had an even higher chance of responding to one of these therapies. This observation requires more research though. Side effects of these drugs were mostly mild or moderate in severity.

Many of these drugs are now being tested in randomized trials compared to second-line chemotherapy drugs such as docetaxel. Other trials of PD-1 and PD-L1 inhibitors are combining them with first-line chemotherapy. Combinations with other immune based therapies such as ipilimumab or tremelimumab are also being tested. These combinations though have seen more side effects though.

Conclusions

A lot of progress has been made in recent years in the field of immune-based therapies. The immune modulating drugs in particular, appear active in NSCLC. However, they remain investigational agents at this time and are only available as part of clinical trials. Trials are ongoing comparing many of these agents with standard treatment options to determine where they might fit in the treatment algorithms for NSCLC. They do appear to offer significant promise in the future for patients with lung cancer.

Sources:

1. Butts C, Socinski MA, Mitchell PL, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. The lancet oncology 2014;15:59-68.

2. Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol 2012;30:2046-54.

3. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. N Engl J Med 2012;366:2443-54.