Immune Checkpoint Blockade: The Hope for Immunotherapy as a Treatment of Lung Cancer?

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Over the past 20 years, immunotherapy has not played a role in the treatment of lung cancer outside of clinical trials. Early trials with vaccines yielded promising results, but phase III trials have yet to show an improvement in survival. Recently, immune checkpoint pathway inhibitors have yielded exciting and consistent activity across this class of antibodies. However, phase III trials are now ongoing. Currently, the hope of bringing immunotherapy to lung cancer patients lies in this class of drugs. Only time will show us if these antibodies will yield an improvement in long-term survival. This review will focus on checkpoint pathway inhibitors that have completed early-phase trials.

Immunotherapy has yet to find its place in the treatment of lung cancer. Vaccines once thought to be the mainstay of immunotherapy have yet to yield an improvement in long-term survival in lung cancer. Even as recently as 2013, a vaccine, liposomal-BLP25, used in the ideal setting in low-volume disease after definitive therapy did not show a survival advantage compared to placebo.[1] Other vaccines remain in phase III trials and their results are awaited. The largest trial conducted in the adjuvant setting in non-small cell lung cancer (NSCLC) using the MAGE-A3 vaccine is one such trial. Thus NSCLC continues to be considered a non-immunogenic tumor by many.

NSCLC is able to thwart the immune system through many mechanisms. One such mechanism is through aberrant major histocompatibility complex (MHC) class I expression. MHC class I molecules are required for antigen presentation to cytotoxic T cells. Without MHC class I antigens, tumors are able to escape cell lysis by these T cells.[2] Aberrant MHC class I expression can occur via deficiency or lack of expression of MHC molecules.[3,4] Another way that NSCLC can thwart the immune system is by adapting immune inhibitory pathways called immune checkpoints. Some checkpoints are costimulatory. These costimulatory pathways are required for T-cell activation such as CD 28 and its ligands B7.1 (CD80) and B7.2 (CD86).[5] Other checkpoints inhibit T-cell activation such as cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) immune checkpoints.

CTLA-4 is a checkpoint pathway that is important early on in T-cell activation.[5] Through upregulation of CTLA-4, it is able to out compete for its ligands (B7.1 and B7.2) with the costimulatory receptor CD28 after which effector T-cell response is decreased. Regulatory T cells are also known to upregulate CTLA-4 that suppresses activation and expansion of cytotoxic T cells.[6,7] CTLA-4 is only known to be upregulated on T cells and its ligands are expressed on antigen-presenting cells (APC). Preclinically, CTLA-4–deficient mice are known to die early in life from widespread autoimmune syndromes.[8]

Another key checkpoint receptor is PD-1. PD-1 is known to be expressed on activated T cells and mediates immune suppression. In the periphery, the PD-1 receptor binds to its ligands PD-L1 (B7-H1) and PD-L2 (B7-DC), which can be expressed on APCs, as well as tumor cells.[9] Binding of PD-1 with its ligands results in downregulation of activated T cells. Preclinically, PD-1–deficient mice are known to develop modest strain and organ-specific autoimmunity later in life.[10] Tumors are able to coopt the PD-L1 ligand to use it to bind to PD-1 and thus able to downregulate the immune response.[11]

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Financial disclosure: Advisory board member and/or consult for Bristol Myers Squibb (uncompensated) and Merck (compensated).
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0093-7754/ - see front matter

http://dx.doi.org/10.1053/j.seminoncol.2013.12.014

ANTI–CTLA-4 INHIBITORS

Antibodies have been developed to block the CTLA-4 pathway by binding to the CTLA-4 receptor. By blocking CTLA-4, this allows binding of B7.1 to its costimulatory receptor CD28 that causes an overriding stimulatory signal and T-cell activation.[12] CTLA-4 blockade is analogous to releasing the breaks on the immune system. Two different antibodies have been developed to block CTLA-4. Currently, ipilimumab is being studied in phase III trials in combination with chemotherapy in both NSCLC and small cell lung cancer (SCLC).

Ipilimumab

Ipilimumab is an anti–CTLA-4 antibody that is approved for use in melanoma and also has been tested in combination with chemotherapy in NSCLC. In a randomized phase II trial of patients with never-treated stage 4 NSCLC, patients were randomized to either combination chemotherapy (paclitaxel 175 mg/m^2 and carboplatin [AUC 6]), or the same chemotherapy combined with ipilimumab (10 mg/kg) given once every 3 weeks either in combination with cycle 1 through cycle 4 (concurrent regimen) or starting later with cycle 3 and continuing on through cycle 6 (phased regimen)[13] (Table 1) The trial enrolled 204 patients. A total of 73 patients were treated with all six cycles of combination therapy and continued on ipilimumab or placebo once every 12 weeks until cancer progression during the maintenance phase of the trial. The primary endpoint of immune related progression-free survival (irPFS) took into account the ability of immune-based therapy to initially cause a tumor flare or growth followed by response. Improvement in irPFS was noted in favor of the phased arm compared to chemotherapy, hazard ratio (HR) of 0.72 ($P = .05$). An improvement in survival was also noted in the patients treated on the phased arm, but this was not statistically significant (median overall survival [OS] of 12.2 months compared to 8.3 months). The concurrent arm did not result in an improvement in irPFS or OS. Differences in irPFS and OS were noted by histology in a preplanned subset analysis. Squamous cell carcinoma patients who were treated with the phased treatment had a significantly improved irPFS (HR 0.55; 95% confidence interval [CI], 0.27–1.12) and OS (HR 0.4; 95% CI, 0.22–1.03). The patients with nonsquamous cell carcinoma did not benefit with the addition of ipilimumab. The modified World Health Organization (WHO) best overall response rate (ORR) was 32% in the phased arm compared to 14% in the chemotherapy along arm. The immune-related ORR was 32% in the phased schedule compared to 18% for chemotherapy alone. The concurrent schedule yielded a response rate of 21% and immune-related ORR of 21%.

Ipilimumab did not add significant toxicity to chemotherapy. In general, the grade 3 or 4 side effect rate was similar across all arms with the rate in the control arm of 27%, concurrent 41%, and phased arm 39%. Only 6% of patients in the phased arm had to discontinue the drugs due to related side effects. Two treatment-related deaths were noted, one in the control arm due to neutropenic sepsis and one in the concurrent treatment arm due to septic shock. Based on these results, further testing using the phased schedule of giving ipilimumab in combination with paclitaxel and carboplatin is planned in patients with metastatic squamous carcinoma of the lung. This international trial is enrolling 920 patients with a primary endpoint of survival (Table 2).

The phase II trial described above also included patients with SCLC.[14] Again, the phased regimen improved irPFS but not OS. The median irPFS of the phased regimen treated group was 6.4 months compared to 5.3 months for the chemotherapy-treated patients. The resulting HR was 0.64 ($P = .03$). The OS was 12.9 months for the phased ipilimumab-treated group compared to 9.9 months for the chemotherapy-treated group. The patients treated with the concurrent ipilimumab regimen did not improve their irPFS or OS compared to control. Tumor response favored the phased regimen again with a modified WHO best ORR of 57% versus 49% in the control arm. Now a phase III trial for patients with metastatic SCLC is combining the standard small cell regimen of platinum and etoposide with ipilimumab using the phased regimen compared to the standard chemotherapy alone. This trial is ongoing[15] (Table 2)

Tremelimumab

Another anti–CTLA-4 antibody is tremelimumab. Tremelimumab is a fully human immunoglobulin G2 (IgG2) antibody. In one phase II study performed in lung cancer patients with stable or responding disease after first-line chemotherapy, it was compared to observation as maintenance therapy.[16] The PFS was not significantly improved. At the time, future development in NSCLC was placed on hold, but now trials combining it with the MEDI-4736 anti–PD-L1 antibody are planned[17] (see details below).

ANTI–PD-1 AND PD-L1 INHIBITORS

Antibodies have been developed to block the interaction between the PD-1 receptor and its ligand, PD-L1[18] (Table 1) At this time, there are two different ways of blocking the PD-1 pathway (Figure 1). Blockade of PD-L1 inhibits the binding of PD-L1 to its