The State of the Art in Non–Small Cell Lung Cancer Immunotherapy

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Once considered an ineffective modality in lung cancer, immunotherapy has emerged as one of the most promising therapeutic strategies for this lethal disease. The past few years have seen a plethora of clinical trials evaluating various immunotherapeutic approaches in lung cancer. This article discusses the current status of immunotherapy in non–small cell lung cancer with a review of completed studies and ongoing trials.

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INTRODUCTION

The past decade has seen major developments in the treatment of lung cancer. Despite this, it remains the most common cause for cancer deaths across the globe. In the United States, lung cancer comprises 14% of cancer diagnoses and 27% of cancer deaths.[1] Non–small cell lung cancer (NSCLC) is the most common type constituting approximately 84% of all lung cancers. In the past years, tremendous efforts have been directed toward identifying targetable molecular alterations in NSCLC. Targeted therapeutic agents, based on genetic mutations and activated signaling pathways in NSCLC, have added significantly to our treatment armamentarium while minimizing drug toxicity.[2,3] However, more than half of the lung cancer cases do not have an identifiable target, and therapeutic strategies are applicable only to 20% of all cases.[4] Thus, cytotoxic chemotherapy, which has moderate efficacy and significant toxicity, is still the only therapeutic option for most patients.

Novel strategies that are effective in treating larger proportion of patients with NSCLC while minimizing treatment-related toxicities are particularly enticing. Immunotherapy has recently emerged as one such promising treatment strategy. Advances in the understanding of the mechanisms that regulate immune responses in cancer have led to several rationally designed immunotherapeutic strategies in NSCLC.

Cancer immunotherapy is generally classified as either passive or active. Passive immunotherapy alludes to immunologic interventions that do not use the host immune machinery for activity. Active immunotherapeutic approaches, by contrast, are aimed at modulating the host's immune machinery to fight cancer.

PASSIVE IMMUNOTHERAPY

The most important interventions in this category include monoclonal antibodies to ligands, and receptors involved in cancer signal transduction pathways and adoptive T-cell transfer.

Monoclonal Antibodies

These agents demonstrate antitumor activity through various mechanisms including antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity.[5] Agents in this category that are relevant to lung cancer include vascular endothelial growth factor inhibitor, bevacizumab,[6] and epidermal growth factor receptor inhibitor, cetuximab.[7]

Adoptive T-cell Transfer

This typically involves identification, isolation, ex vivo amplification, and subsequent infusion of autologous tumor-infiltrating T cell or lymphokine-activated killer cell therapy.[8] This form of therapy has been used with or without coadministration of

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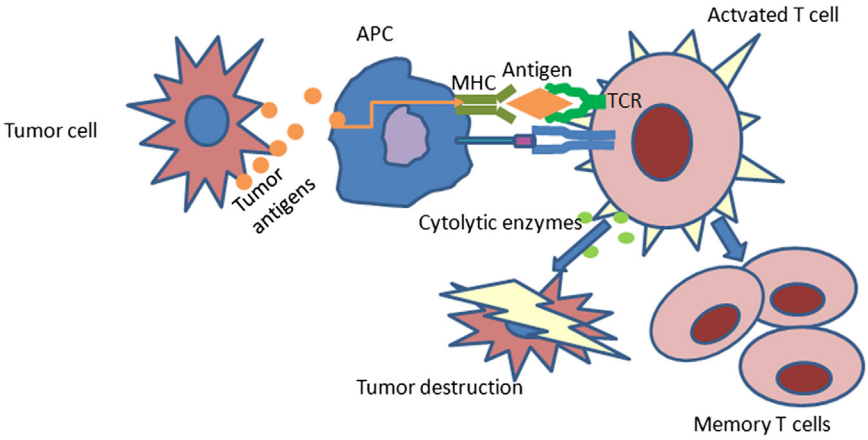

Figure 1. Tumor-specific T-cell response. Antigen-specific immune responses are dependent on tumor antigen presentation on major histocompatibility (MHC) molecules by antigen presenting cells (APCs). This process triggers expression of B7 on the APCs, which then migrate to lymph nodes. Within the lymph node, the APCs present tumor antigen to resting T cells though their interactions with the antigen-specific T-cell receptor (TCR). Additional interaction between B7 on the APC and CD28 on the T cell results in T-cell activation and its entry into circulation. When the activated T cell comes into contact with tumor and recognizes antigens expressed on the tumor in association with MHC, it releases cytolytic enzymes (perforin and granzyme) and cytokines. This eventually leads to tumor destruction and creation of memory T cells and is the primary principle behind development of cancer vaccines. (Color version of figure is available online at http://www.semthorcardiovascsurg.com.)

growth factors to enhance T-cell response.[8] A few phase II studies are now underway exploring this modality as a therapeutic approach in multiple cancers, including lung, for example, a phase II trial is testing the activity of T cells genetically engineered to target carcinoembryonic antigen in patients with carcinoembryonic antigen-expressing adenocarcinomas.[9]

ACTIVE IMMUNOTHERAPY

These approaches are primarily aimed at induction of antigen-specific T-cell response and are based on the premise that the immune system plays a key role in surveillance and eradication of malignancy.[10] Many cancers are associated with genetic alterations that result in production of neoantigens that can potentially be recognized by the immune system as foreign and elicit a T-cell mediated immune response (Fig. 1).[10-12] Paradoxically, physiological checks and balances that work throughout the immune cascade to control antigen hyperresponsiveness such as checkpoint pathways, immunosuppressive cytokines, antigen-presenting cell (APC) senescence, and regulatory T cells tend to create a permissive environment for tumor growth and present a major challenge to successful development of immunotherapy.[12]

Traditionally considered a relatively nonimmunogenic cancer, immune modulation as a potential therapeutic approach in lung cancer was suggested by some observational studies, which reported that immune response induced by local inflammation may influence the prognosis of lung cancer.[13] Early attempts at lung cancer immunotherapy that focused on nonspecific immune stimulants, such as bacille Calmette-Guerin,[14] thymosin,[15] and *Corynebacterium parvum*,[16] as well as nonspecific immune responses induced by agents such as interleukin-2,[17] were largely unsuccessful. Subsequent discovery that NSCLC is immunogenic and can express tumor-associated antigens[18] has led to the development of several active immunotherapy protocols. Active immunotherapeutic approaches namely cancer vaccines, and checkpoint blockade inhibitors (cytotoxic T-lymphocyte antigen-4 [CTLA-4] and programmed death-1 [PD-1]/programmed death ligand-1 [PD-L1]) and their current status in lung cancer treatment armamentarium are reviewed in the subsequent sections.

Lung Cancer Vaccines

A multitude of clinical trials evaluating vaccines have been conducted in NSCLC, but most of the initial studies were disappointing. Some of the reasons that could have resulted in their failure include inability to elicit potent CD4+ and CD8+ T-cell responses, while overcoming the mechanisms of tumor-induced immune tolerance, lack of tumor specificity, and lack of ideal supportive components such as adjuvants and delivery systems.[18] Several new strategies that address these earlier shortcomings have now entered phase III clinical trials, and