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Overview

Immune Checkpoint Inhibitors in Lung Cancer – An Unheralded Opportunity?

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Abstract

Lung cancer remains the leading cause of cancer-related death worldwide, with non-small cell lung cancer accounting for 85% of the disease. Over 70% of patients present with locally advanced, non-resectable or metastatic disease and despite improvements in chemoradiotherapy regimens and the development of molecularly targeted agents, 5 year survival rates remain poor, with acquired resistance to novel targeted therapies becoming a growing concern. Currently there remains an unmet need in effectively treating and inducing durable responses in advanced disease. Targeting the immune system has, however, recently given hope of improving therapeutic outcomes for these patients. The notion that the immune system is capable of recognising and eliminating cancer cells is now a widely accepted phenomenon and growing evidence suggests lung cancer is an attractive target for such intervention. Recent success targeting the programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) axis of immune checkpoint inhibition suggests a major immunotherapeutic advance in treating lung cancer and unheralded opportunity for such approaches to further improve outcome for patients.

Currently there is considerable interest in combining anti-PD-1 or PD-L1 monoclonal antibodies with established standard of care therapies such as radiotherapy. Radiotherapy is known to be immunostimulatory and efforts are underway to combine and augment the efficacy of the immune checkpoint inhibitors further. This review outlines the interaction between lung cancer and the immune system, summarises current evidence supporting the use of monoclonal antibodies targeting the PD-1 axis in lung cancer and explores the potential of combining radiotherapy with immunotherapy to augment anti-tumour immune responses.

Key words: Immune checkpoint; immunotherapy; non-small cell lung cancer; programmed death-1; radiotherapy; tumour microenvironment

Statement of Search Strategies Used and Sources of Information

This review is based on a search of peer-reviewed articles found on Pubmed and Google Scholar databases. Search terms included non-small cell lung cancer, radiotherapy, immunotherapy, immune checkpoint inhibitors. Individual bibliographies were reviewed for additional references and information regarding clinical trials was obtained from the international clinical trials registry.

Introduction

Following the increasing popularity of smoking, the incidence of lung cancer has risen precipitously throughout the 20th century to become the most prevalent cancer worldwide. More than 1.8 million new cases were diagnosed in 2012 alone and despite novel chemoradiotherapy combinations, lung cancer remains the leading cause of cancer-related death worldwide [1].

Non-small cell lung cancer (NSCLC) constitutes 85% of all diagnosed lung cancers [2], with the mainstay of curative therapy comprising surgical resection and adjuvant

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platinum-based chemotherapy offering 5 year survival rates of about 60–70% in stage I disease [3,4]. However, over 70% of patients present with locally advanced non-resectable disease (where standard of care is chemoradiotherapy) [5] or metastatic disease (where standard of care is chemotherapy or targeted therapies in patients with driver mutations) [6]. Progress in chemoradiotherapy and systemic therapy regimens have, however, only offered modest improvements to survival in locally advanced and advanced disease, with 5 year survival rates just below 10% in the UK [7,8].

The discovery of molecular pathways and their associated driver mutations, which promote lung cancer growth, has more recently identified numerous key targets for novel therapeutic intervention. Specific mutations in epidermal growth factor receptor and the anaplastic lymphoma kinase fusion gene are present in 4–10% of patients [9]. Tyrosine kinase inhibitors show clinical benefit in patients with such mutations [10]. However, almost all patients eventually acquire resistance, limiting the efficacy of such therapies in advanced disease [11–13]. In locally advanced disease, both local relapse and metastatic disease progression after definitive chemoradiotherapy are the dominant cause of death after initial therapy [5]. Therefore, novel more effective therapeutic approaches are urgently required.

An exciting area of current development is the use of immunotherapeutic strategies, designed to activate tumour-specific cytotoxic T-cells, which can eliminate existing disease and generate long-term immunological memory.

The Immune Contexture of Lung Cancer

Clear evidence now shows that the presence of tumour-infiltrating CD8+ T-lymphocytes is a positive prognostic indicator in a range of cancer types, including NSCLC [14,15]. Several studies evaluating T-cell infiltration in resected NSCLC tumours have shown that high infiltration of both CD4+ and CD8+ T-cells into lung tumours is an independent favourable prognostic indicator in a variety of disease stages for both treatment naive patients and those receiving adjuvant chemotherapy [16–18]. Consequently it is increasingly recognised that the composition of the immune infiltrate in NSCLC, as well as other cancer types, can provide an ‘immunoscore’, which although is currently yet to be proven as superior, can serve as an additional prognostic indicator to the traditional tumour-node-metastasis staging system in NSCLC [15,19].

However, although tumour cells are clearly visible to the immune system, in the majority of patients, effective T-cell-mediated immunity is inhibited by the profoundly immunosuppressive tumour microenvironment (TME). The TME comprises a network of cellular and molecular mechanisms of resistance, including soluble factors such as prostaglandin E2, transforming growth factor-β and interleukin-10 [20–22] and regulatory immune cells, including myeloid-derived suppressor cells, regulatory T-cells and tumour-associated macrophages [23–25]. Furthermore, a principal mechanism of immune evasion exploited by tumour cells is to co-opt co-inhibitory immune checkpoints, which negatively regulate T-cell activity [26].

Immune Checkpoints

The upregulation of co-inhibitory immune checkpoints on activated T-cells is a physiological process that helps to maintain self-tolerance and prevent autoimmunity [26,27]. However, this mechanism of regulation is frequently exploited by tumours that stimulate the immune system continuously with a plethora of antigenic material. Consequently multiple co-inhibitory immune checkpoints and their associated ligands are persistently upregulated on the surface of tumour-infiltrating T-lymphocytes, other immune cells and cancer cells [26]. Two key checkpoints have emerged as leading therapeutic targets across a range of cancer types, including NSCLC: cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed death-1 (PD-1)/PD-ligand 1 (PD-L1). CTLA-4 and PD-1/PD-L1 regulate distinct phases of T-cell activation. CTLA-4 is expressed on activated T-cells and has a high affinity for B7 family co-stimulatory ligands, CD80 and CD86, expressed on antigen-presenting cells. Ligation by CTLA-4 competitively displaces binding of the co-stimulatory receptor CD28, attenuating T-cell activation [26,28]. PD-1/PD-L1 interactions provide an inhibitory signal during the effector phase of T-cell response, inhibiting CD8+ T-cell survival, effector function and inducing Fas-mediated T-cell apoptosis [29–31]. Cancer cells are known to upregulate surface PD-L1 expression in response to attack by interferon-gamma (IFN-γ)-producing T-cells; so-called ‘adaptive resistance’ [32].

Monoclonal antibodies (mAb) directed against the CTLA-4 immune checkpoint first showed evidence of improved overall survival for the treatment of patients with metastatic melanoma [33]. By contrast, the use of CTLA-4 mAb as a single agent in NSCLC has failed to show superiority over best supportive care [34] and has yielded only modestly improved immune-related progression-free survival (PFS) with a significant toxicity profile when used in combination with chemotherapy in advanced disease [35].

More prevalent in NSCLC is the PD-1 immune checkpoint with its associated ligand PD-L1. PD-1 is upregulated on tumour-infiltrating T-cells in NSCLC and is associated with reduced antigen-presenting cell maturation and T-cell infiltration [36–38]. Its ligand, PD-L1, is abundant in the lung TME and early studies described cancer cell expression levels in resected NSCLC tumours of 95–100% [30,39]. However, PD-L1 expression is not limited to the tumour itself and is also expressed by regulatory T-cells and other non-T-cell populations present in the TME [29,40].

Given this background it is not surprising that the PD-1/PD-L1 axis represents a tremendous therapeutic opportunity in NSCLC. Therapies that target either PD-1 (e.g. nivolumab, pembrolizumab) or PD-L1 (e.g. durvalumab, atezolizumab and avelumab) may alter the immune contexture of the immunosuppressive TME, overcome

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