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Overview

Radiotherapy and Immunotherapy Combinations in Non-small Cell Lung Cancer: A Promising Future?

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Abstract

The goal of re-programming the host immune system to target malignancy with durable anti-tumour clinical responses has been speculated for decades. In the last decade such speculation has been transformed into reality with unprecedented and durable responses to immune checkpoint inhibitors seen in solid tumours. This mini-review considers the mechanism of action of immune modulating agents and the potential for combination with radiotherapy in the treatment of non-small cell lung cancer.

Key words: Checkpoint inhibition; immunotherapy; NSCLC; radiotherapy

Statement of Search Strategies Used and Sources of Information

The terms 'immune checkpoint inhibition', 'immune checkpoint inhibitors', 'PD-1 inhibition' and 'radiotherapy' together with their derivatives were used to search PubMed. All relevant studies relating to radiotherapy and immune checkpoint inhibition combinations in lung cancer were included in the preparation of the overview. No limitations were placed on language or year of publication. To identify relevant clinical trials, the ClinicalTrials.gov website was searched under the search terms 'Pembrolizumab and Radiotherapy' and 'Nivolumab and Radiotherapy'.

Introduction

The goal of re-programming the host immune system to target malignancy with durable anti-tumour clinical responses has been speculated for decades [1]. However, only over the last decade has the use of immune modulating agents delivered meaningful clinical responses that have led to great promise in the treatment of lung cancer as well as other solid malignancies [2]. This mini-review outlines the mechanism of action of immune modulating agents and the potential for combination with radiotherapy in the treatment of non-small cell lung cancer (NSCLC).

Immunotherapy in Lung Cancer

Immunotherapeutic strategies can be broadly considered as either passive or active. Passive approaches delivered the initial major clinical advances with the introduction of the anti-CD20 monoclonal antibody rituximab, which was the first monoclonal antibody licensed in the treatment of cancer in 1997, followed closely by trastuzumab, which targets and binds to the extracellular domain of the HER-2/neu receptor, which interferes with receptor function and expression [2,3]. Active immunotherapy approaches include non-specific immune modulation (use of interleukin and interferon), therapeutic vaccines (e.g. MAGE-A3 vaccine), modulation of T-cell function and oncolytic viruses and have been slower to show clinical efficacy [4–6]. However, it is the modulation of T-cell function with the

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immune checkpoint inhibitors that modulates the anti-CTL antigen-4 (CTLA-4) and the anti-programmed death-1 (PD-1) ligand function that has particularly attracted interest over the last 5 years, with durable clinical responses being seen in malignant melanoma, renal cell carcinoma and NSCLC, among other tumour types [7].

For many years it has been known that tumours can evade and escape the immune system by a range of immune effector cells such as T regulatory cells, myeloid deprived suppressor cells, tumour associated macrophages and via the production of a range of immunosuppressive cytokines (e.g. interleukin-10, transforming growth factor-beta, PGE2 and interferon-γ) within the tumour microenvironment, which lead to suboptimal priming of dendritic cells and a tolerogenic phenotype [8–10]. A key mechanism of immune evasion is known to be the direct inhibition of cytotoxic T-cells. T-cell activation is a two-step process, with the first being antigen recognition by the T-cell receptor and the second the generation of an antigen-independent co-regulatory signal that determines whether the T-cell will be switched on or off in response to the antigen. This second step is overseen by the immune checkpoint pathways, which are either stimulatory or inhibitory. More recently these biological insights about the nature of immune checkpoint inhibitors have led to an increasing number of therapeutics with an intense focus on the PD-1-PD-L1 axis. PD-1 is an inhibitory receptor expressed on T-cells is key to preventing the development of autoimmune disease and it is thought that the function of PD-1 is to limit normal tissue damage in the presence of inflammation [11,12]. PD-L1 and PD-L2 are ligands of PD-1 and these bind to PD-1 to inhibit T-cell function. Upregulation of PD-L1 and PD-L2 is common in many tumour types and is associated with a poorer prognosis [13]. A number of PD-L1 and PD-L2 inhibitors have been shown to be effective across a range of tumour sites [7]. Two agents, pembrolizumab and nivolumab, have been shown in randomised trials to be superior to chemotherapy in the second-line treatment of NSCLC [14–16]. In a randomised study comparing docetaxel versus pembrolizumab as second-line therapy in patients with advanced NSCLC who expressed PD-1, those who received pembrolizumab 10 mg/kg had a median overall survival of 17.3 months as compared with 8.2 months with docetaxel ($P < 0.0001$) [14]. Similarly, in a study comparing nivolumab versus docetaxel in second-line non-squamous NSCLC, those who received nivolumab had a 1 year survival of 19 months compared with 8 months for those who received docetaxol [16]. Also, importantly in the setting of second-line treatment for NSCLC, this increase in survival did not come at the expense of increased toxicity in these studies. For example, in the study of nivolumab versus docetaxel in non-squamous NSCLC, treatment-related adverse events of grade 3 or 4 were seen in 10% of those treated with nivolumab, as compared with 54% of those treated with docetaxel [16]. The results from checkpoint inhibition in NSCLC have led to the hope that these agents may improve outcomes in a range of different treatment indications and in early as well as late stage NSCLC.

The Potential of Radiotherapy with Immunotherapy Combinations

Despite the excitement of durable remissions seen in the three key studies using immune checkpoint inhibitors in lung cancer, the response rates were low (18–20%) with only a minority of patients achieving a response [14–16]. The key focus in radiobiology over the last decades has been the mechanism of radiotherapy-induced tumour cell death and research on radiation-induced damage to cell structures mediated by free radicals, leading to the production of DNA double-strand breaks, which in turn lead to apoptosis, if not repaired [17–19]. However, as our understanding of the effects of radiotherapy has increased it has been recognised that radiation has effects on the vascular system, the tumour stroma and the host immune response. The impact that radiotherapy is known to have on the generation of tumour-specific immunity includes enhanced antigen release, expression of NK2GD ligands, complement deposition, production of type I interferon, increased major histocompatibility complex and neo-antigen expression and the induction of immunogenic cell death [20–24]. Other elements of immunogenic modulation include changes in the mechanism of antigen presentation and translocation of calreticulin to the cell surface [25,26]. Thus, radiotherapy may act as a primer for or stimulus to initiate or augment an immune-mediated anti-tumour response.

Despite the ability of radiotherapy to induce local immune responses, the generation of systemic anti-tumour immunity that leads to clinical responses outside of the irradiated tumour area (the abscopal effect) is rare in clinical practice [27]. This lack of abscopal effects is thought to be secondary to the nature of the immuno-suppressive tumour microenvironment outlined above. Numerous preclinical studies have, however, confirmed that systemic anti-tumour immune responses can be generated using radiotherapy and immunomodulatory agents [7].

Recently there has been increasing interest in the translation of these findings to the clinic, which has been fuelled by a number of provocative case reports and phase II studies [28–31]. Overall, these results suggest that radiotherapy after immunoregulatory agents may lead to abscopal responses in some patients, providing optimism that radiotherapy can enhance the systemic anti-immune response. The premise is that radiotherapy delivered to the tumour seems to be able to enhance anti-tumour immunity by inducing tumour antigen expression and liberating tumour antigen from dying tumour cells and thus activating anti-tumour immune responses. These local radiotherapy-induced immune responses, however, need to be augmented with the addition of immune checkpoint inhibitors, which enhance the local and systemic immune response by overcoming the tumour-induced T-cell inhibition and immune suppression [32]. Thus, combining radiotherapy with inhibitors of PD-1 or PD-L1 seems to be an attractive option to enhance the effectiveness of either treatment [33]. Given the durable remissions seen with anti-PD-1/PD-L1 monoclonal antibody for some patients with NSCLC and the important role played by radiotherapy in the