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Combining chemotherapy with PD-1 blockade in NSCLC

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ABSTRACT

Antitumor immunity relies on the ability of the immune system to recognize tumor cells as foreign and eliminate them. An effective immune response in this setting is due to surveillance of tumor-specific antigens that induce an adaptive immune response resulting in T-cell mediated cytotoxicity. Immune checkpoint inhibitors, specifically those targeting the programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) axis, have demonstrated promising activity in non-small cell lung cancer (NSCLC). However, there remains a crucial need for better treatment strategies for the majority of patients with advanced NSCLC, particularly in the frontline setting. Chemotherapy can increase antigenicity via immunogenic cell death (ICD) of tumor cells as well as also reduce "off target" immunosuppression in the tumor microenvironment (TME). Combining chemotherapy with PD-1 blockade harnesses the potential synergy between these agents and has led to encouraging results in the up-front treatment of NSCLC. In this review, we summarize the preclinical rationale behind these combinations and review recent trial data demonstrating their efficacy.

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1. Introduction

Lung cancer is the most common cancer and leading cause of cancer related death worldwide, accounting for >1.6 million cases and 1.3 million deaths annually (Ferlay et al., 2010). For patients with advanced stage non-small cell lung cancer (NSCLC), the most common form of lung cancer in the United States, platinum-doublet chemotherapy (PT-DC) improves outcomes with an objective response rates (ORR) of approximately 26%. Unfortunately, durable disease control is disappointingly rare – fewer than 5% of patients are alive 5 years later and median survival is ~10 months (Delbaldo et al., 2004; Spiro, et al., 2004). Treatment with immune checkpoint inhibitors that block inhibitory T-cell signaling has dramatically improved outcomes for previously treated advanced NSCLC. However, as these agents move into the frontline management of metastatic NSCLC, better strategies are needed to broaden their reach beyond the minority of tumors that express high levels of programmed death ligand 1 (PD-L1). In unselected patients, single agent PD-1 blockade has limited activity with objective response rates (ORRs) of 15–25% (Antonia et al., 2016; Besse et al., 2015; Garon et al., 2015; Gettinger et al., 2015). Certain chemotherapeutic agents can augment antitumor immunosurveillance and enhance subsequent effector T-cell activity and tumor cell death. Combining immunogenic chemotherapy with immune checkpoint

Abbreviations: NSCLC, non-small cell lung cancer; PT-DC, platinum-doublet chemotherapy; ORR, objective response rate; PD-1, programmed cell death-1; PD-L1, programmed death ligand-1; CTLA-4, cytotoxic T-lymphocyte antigen-4; DC, dendritic cell; TME, tumor microenvironment; PFS, progression-free survival; OS, overall survival; AE, adverse effect; CM, CheckMate; KN, KEYNOTE; CRT, chemoradiotherapy.

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blockade can drive deeper, sustained tumor responses. In this report, we review the molecular basis for these treatment combinations and trial data demonstrating their efficacy in advanced, untreated NSCLC.

2. Innate and adaptive antitumor immune responses

The molecular identification and elimination of tumor cells that have escaped cell-intrinsic tumor suppressor mechanisms forms the basis of cancer immunosurveillance (Burnet, 1970). Most tumor cells express cancer-specific peptides or neoantigens generated by unique mutations that can be recognized by antigen-specific receptors and trigger a cytotoxic T-lymphocyte (CTL) response (Gajewski, Schreiber, & Fu, 2013; Monach, Meredith, Siegel, & Schreiber, 1995; Topalian et al., 1992; van der Bruggen et al., 1991). The innate and adaptive arms of the immune system synergistically function to maintain immunosurveillance. The adaptive immune system, which consists of B and T cells, recognizes tumor neoantigens via clonally expressed B- and T-cell receptors.

However, to generate robust adaptive immune responses, antigen-presenting cells (APCs) of the innate system, including macrophages, monocytes, and dendritic cells (DCs), provide crucial stimulatory signals for efficient expansion of T-cells. This activated T-cell population is composed of both $CD8^+$ CTLs that drive effector responses and $CD\text{-}4^+$ helper T cells that provide costimulatory signals to B-cells, leading to affinity maturation, isotype switching, and subsequent antibody production. In addition to antigen presentation, the innate immune system can produce rapid inflammatory responses on a non-clonal basis in response to signals from pattern recognition receptors (PRR) such as Toll-like receptors (TLRs) or NOD-like receptors (Apetoh et al., 2007; Caruso, Warner, Inohara, & Núñez, 2014). This can result in an inflamed tumor microenvironment (TME) that further attracts T-cells (Pages et al., 2010). However, despite these well-coordinated mechanisms, tumor cells often evade elimination.

Intriguingly, tumors that develop in the absence of an intact immune system are often more immunogenic than those arising in immunocompetent hosts (Shankaran et al., 2001). This finding raises issue with the classical concept of cancer immunosurveillance and serves as the basis of the cancer immunoediting hypothesis. This notion describes a dual, paradoxical role for the immune system in both protecting against tumor formation while also sculpting tumor immunogenicity through the selection of poorly immunogenic cancer cells (Dunn, Old, & Schreiber, 2004).

Tumors can also evade immune elimination by nurturing a complex, immunosuppressive TME. This network, composed of cancer cells, stromal cells, and other inflammatory cells, upregulates inhibitory T-cell signaling via receptors such as cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1), Lymphocyte Activation Gene-3 (LAG-3), and T-cell Immunoglobulin and Mucin protein-3 (TIM-3) that physiologically serve to limit overstimulation of the immune system after antigen encounter (Nirschl & Drake, 2013). As a result, CTLs in the TME display poor cytokine production and decreased proliferation characteristic of an "exhausted" phenotype (Jiang, Li, & Zhu, 2015). Importantly, in vitro stimulation of these "exhausted" T cells can restore their functional properties, suggesting that the observed dysfunction is reversible (Rosenberg & Dudley, 2009).

One such reversal mechanism involves blocking co-opted inhibitory checkpoints such as PD-l through the use of monoclonal antibodies. PD-1 is expressed on activated T cells, B cells and natural killer (NK) cells, while its ligand, PD-L1 is expressed by tumor cells and immune cells (Hirano et al., 2005). Upon ligand binding, PD-1 forms clusters with T cell receptors (TCRs), leading to their suppression and subsequent T-cell inactivation (Yokosuka et al., 2012). Antibodies blocking the PD-1/L1 axis have transformed NSCLC treatment over the past decade; however, only a small subset of patients generally respond to anti-PD-1/L1 therapy, prompting strategies to further improve their antitumor efficacy.

3. Chemotherapy and immune modulation

Cytotoxic chemotherapy primarily functions to arrest tumor growth by blocking cell division. However, certain chemotherapies can enhance antitumor immune responses through a variety of mechanisms (Gotwals et al., 2017). One of these involves the induction of immunogenic cell death (ICD), a mechanism of cell death that elicits an inflammatory reaction in response to specific molecular signals released by dying cells, particularly cancer cells (Gotwals et al., 2017). However, not all cell death results in immune activation –normal tissue undergoes a rapid rate of cell turnover that does not provoke an inflammatory response. On the other hand, the death of only a few cells by pathogens with increased antigenicity can trigger a robust antigen-specific immune response (Fuchs & Steller, 2011). ICD is associated with an adaptive stress response that favors maturation of DCs and stimulation of a type I interferon (IFN) response (Gotwals et al., 2017). Chemotherapeutic agents (the best studied of which include cyclophosphamide, anthracyclines, and oxaliplatin) can promote ICD via the release of damage-associated molecular patterns (DAMPs), such as calreticulin (CRT), high mobility group box 1 (HMGB1) and adenosine triphosphate (ATP) (Galluzzi, Buque, Kepp, Zitvogel, & Kroemer, 2015). Upon binding to PRRs on myeloid and lymphoid cells, these DAMPs can generate a robust effector immune response (Fig. 1) (Krysko et al., 2012).

Whether indirectly stimulating the immune system through ICD or directly regulating immune cellular subsets, chemotherapy can have a profound impact on the antitumor immunity. In NSCLC, specific agents such as platinum compounds, taxanes, pemetrexed, and gemcitabine display pleotropic mechanisms of immune modulation.

Cisplatin and carboplatin form the backbone of most doublet NSCLC regimens and act through covalent binding with DNA to form cross-links that impair DNA synthesis and ultimately drive apoptosis (Go & Adjei, 1999). While DNA is classically the major cytotoxic target of platinum agents, part of their antitumor efficacy may also be due to enhancement of T-cell activation by DCs (Hato, Khong, de Vries, & Lesterhuis, 2014). This mechanism is mediated by downregulation of PD-L2 on DCs and tumor cells via the inactivation of STAT6 (Lesterhuis et al., 2011).

Taxanes, on the other hand, can significantly reduce the activity of regulatory T-cells (T-regs) (Chan & Yang, 2000). These $CD4^+CD25^+FOXP3^+$ immune cells play a crucial role in maintaining self-tolerance and immune homeostasis (Zou, 2006). However, their immunosuppressive functions can serve to aid in the growth of neoplastic cells. Through the secretion of inhibitory cytokines such as interleukin-10 and transforming growth factor-beta, T-regs downregulate antitumor responses of $CD4^+$ T-helper and $CD8^+$ cytotoxic T-cells (Rao, Petrone, & Ponath, 2005). Consequently, increased levels of T-regs correlate with greater tumor progression (Ichihara et al., 2003). Treatment with docetaxel can lead to the selective depletion of T-regs and counteract their immune suppression (Li et al., 2014).

Pemetrexed, an antifolate that has direct effects on enzymes involved in cell activation and division, is often used in combination with platinum compounds in nonsquamous NSCLC and mesothelioma. Pemetrexed selectively activates IFN-γ producing natural killer (NK) cells and $CD45RO^+$ memory T cells without increasing the proportion of T-regs (Davis et al., 2012).

Lastly, the pyrimidine analog, gemcitabine, has been shown to reprogram tumor-associated macrophages (TAMs) from an immunoregulatory profile towards an immunostimulatory phenotype (Di Caro et al., 2016).

Together these findings suggest an attractive synergy between cytotoxic chemotherapy and immune checkpoint inhibition. Importantly, most of the preclinical data presented here utilized lower doses of chemotherapy on schedules that are different from those generally employed on clinical practice. This and other factors illustrate some of the challenges that exist when developing rational combinations of chemotherapy and immunotherapy. Nonetheless, a rapidly growing

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