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Review

Not all immune-checkpoint inhibitors are created equal: Meta-analysis and systematic review of immune-related adverse events in cancer trials

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ABSTRACT

Background: Targeting immune checkpoints is a novel approach in cancer therapy. This strategy may trigger immune related adverse events (irAE). We hypothesize that the incidence of irAE will be greater in patients receiving immune checkpoint inhibitors (ICI) targeting only immune cells compared to those that also target tumor cells (PD-L1). In addition, we compared the specific irAE profile and overall response rate (ORR) for each ICI by target(s).

Materials and methods: We reviewed all ICI cancer clinical trials (90; 174 arms) that reported irAE and were published through MEDLINE. 114 arms from 73 trials were eligible for this meta-analysis (including 11,328 patients). We collected and compared arm-specific data including ICI target, number of patients with irAE of any grade, grade 3+ and grade 5, specific irAE, and ORR. The R package "meta" was used to conduct a meta-analysis to calculate and compare the percentage of patients with irAE and ORR.

Results: The incidence (% of patients) of any grade irAE per ICI target was reported for 40 arms (3418 patients) treated with ICI. Most arms (80%) and patients (53%) studied were on phase 1/2 clinical trials. Patients were treated for solid malignancy on 39 arms (97%), mainly melanoma (40%). Two arms included ICI combinations. The incidence of any grade irAE was higher in patients who received ICI targeting CTLA-4 (53.8%) than PD-1 (26.5%) and PD-L1 ICI (17.1%) ($P < 0.001$). Comparative specific irAE rates were calculated for each ICI target.

Conclusions: Our systematic review supported our mechanistic-driven hypothesis. We encourage investigators to report the incidence of irAE in future ICI combination trials.

1. Introduction

The immune system plays an important role in maintaining checks and balance to protect the host from exogenous pathogens by distinguishing "self" from "non-self" (Postow et al., 2015a; Wolchok and Saenger, 2008). However, differentiating between malignant and benign cells is a challenge. The immune system and tumor cells exist in a dynamic state of equilibrium between two extremes (known as immune-editing): the elimination of the tumor by the immune system (T-cell activation) and the ability of the tumor to evade the immune response and proliferate unchecked (tolerance) (Kirkwood et al., 2008). This system involves both stimulatory and inhibitory signals to maintain immune tolerance. Without the latter, the body may eliminate the tumor but will likely develop autoimmune diseases that will destroy self tissues.

In recent years, the blockade of immune inhibitory signals using immune checkpoint inhibitors (ICI) has been approved as a strategy to treat a variety of malignancies such as melanoma (Hodi et al., 2010; Eggermont et al., 2015; Robert et al., 2015a; Weber et al., 2015; Postow et al., 2015b), lung (Borghaei et al., 2015; Garon et al., 2015), head and neck (Seiwert et al., 2016; Ferris et al., 2016), renal cell (Motzer et al., 2015; McDermott et al., 2016) and urothelial (Rosenberg et al., 2016) cancers, as well Hodgkin lymphoma (Ansell et al., 2015). This strategy consists of using one (Hodi et al., 2010; Eggermont et al., 2015; Robert et al., 2015a; Weber et al., 2015; Postow et al., 2015b; Borghaei et al., 2015; Garon et al., 2015; Motzer et al., 2015; Rosenberg et al., 2016;

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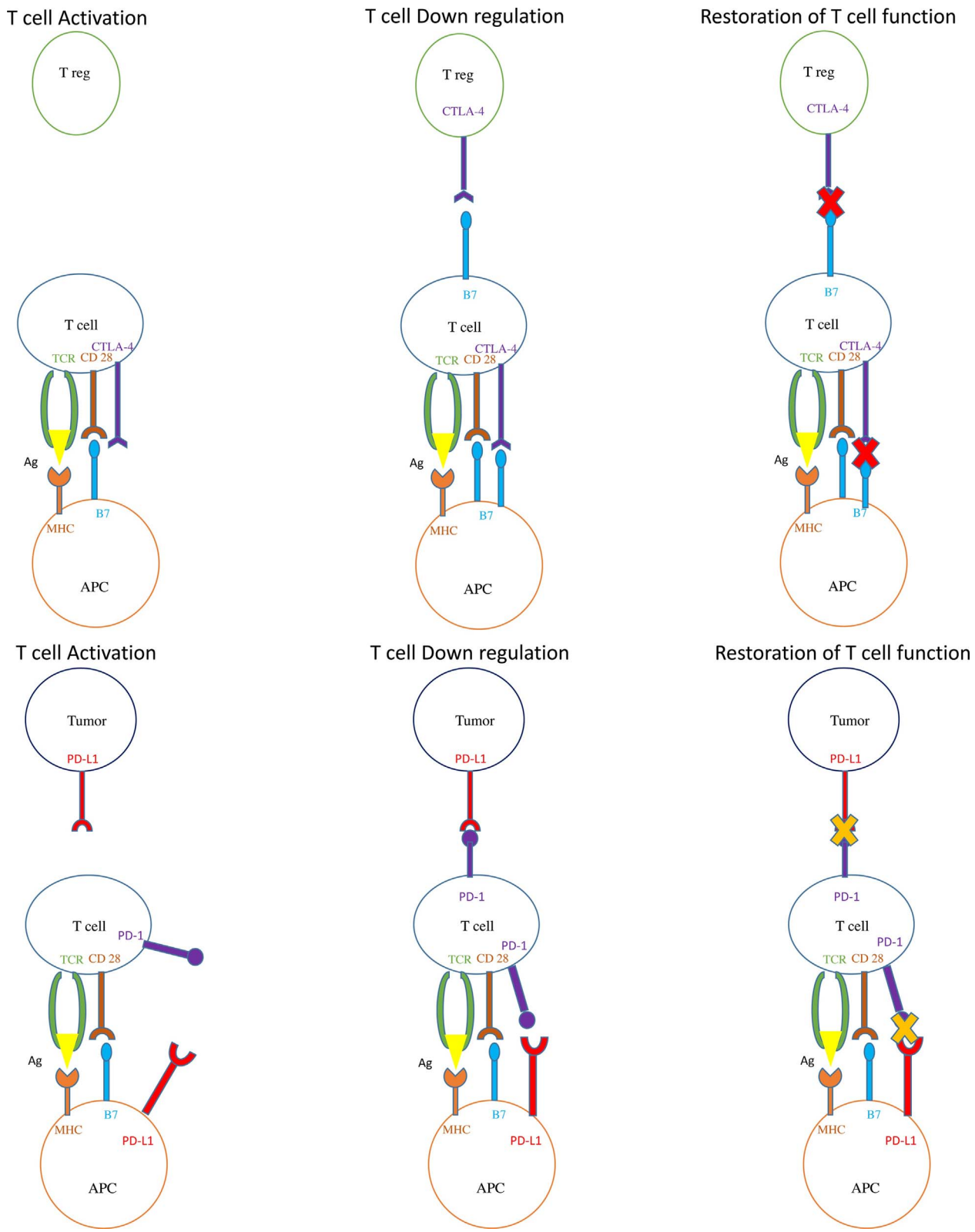

Fig. 1. (a) Mechanism of action of anti-CTLA-4. (b) Mechanism of action of PD-1/PD-L1. APC: Antigen presenting cell; T reg: regulatory T cell.

Ansell et al., 2015; McDermott et al., 2016; Ferris et al., 2016; Seiwert et al., 2016) or two (Postow et al., 2015b; Larkin et al., 2015; Antonia et al., 2016) monoclonal antibodies to target cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), or its ligand (PD-L1) to alleviate tumor-induced immunosuppression of T cells thereby enhancing antitumor effects (Pardoll, 2012). Promising trials are being developed for other cancers (e.g., breast cancer (Spellman and Tang, 2016)) for treatment with ICI.

Immune-related toxicities (irAEs) are a unique aspect of the ICI toxicity profile. These irAEs can affect dermatologic, gastrointestinal, hepatic, pancreatic, pulmonary, renal, endocrine, neurologic, hematologic, ophthalmologic, cardiac, and musculoskeletal organs as well