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Toxicity profiles of immunotherapy☆

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ABSTRACT

Immunotherapies are changing the landscape of advanced solid tumor treatment. These therapies have different mechanisms of action and include oncolytic viruses, checkpoint inhibitors, such as CTLA-4 or PD1/PD-L1 monoclonal antibodies, and CSF-1R antibodies. Given the growing therapeutic impact of these agents in oncology, it is important to better understand their properties. Immunotherapies generate new toxicity profiles that are called immune-related adverse events and require specific management. This review focuses on the mechanisms of action of such side effects, as well as their description and their general management.

Contents

1. Introduction

Immunotherapies are a growing part of the therapeutic arsenal for solid tumors. This trend is evidenced by a number of new immune drugs that were recently approved by the Food and Drug Administration (FDA). Indeed, checkpoint inhibitors (CPIs), such as the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibody ipilimumab and the programmed cell death (PD-1)/programmed cell death ligand 1 (PD-L1) antibodies nivolumab, pembrolizumab and atezolizumab, represent the cornerstone of these new treatments, especially but not exclusively for the treatment of melanoma and non-small cell lung cancer (NSCLC) (Borghaei et al., 2015; Brahmer et al., 2015; Herbst et al., 2016; Hodi et al., 2010; Kaufman et al., 2016; Larkin et al., 2015; Motzer et al., 2015; Rosenberg et al., 2016). Other promising immune agents are being developed, such as oncolytic viruses (OVs) and colony-stimulating factor-1 receptor (CSF-1R) inhibitors. Of note, talimogene laherparepvec (T-VEC) is the first OV to receive FDA approval for the treatment of advanced melanoma patients (Andtbacka et al., 2015; Puzanov et al., 2016). These new agents have different mechanisms of action (Fig. 1) and are responsible for the emergence of specific toxicity profiles, which are commonly called immune-related adverse events (irAEs). Because the use of these agents in daily practice is expected to increase, physicians should be aware of how to manage patients who are treated with such immunotherapies. Indeed, despite the relatively low rates of high-grade side effects with these molecules (usually <10%), some side effects can be life-threatening and require urgent and appropriate management (Weber, Antonia, et al., 2015). This review focuses on the side effect profiles of OVs, CPIs and CSF-1R inhibitors, including their description, their mechanisms of action, and appropriate management.

Abbreviations: AEs, adverse events; AI, auto-immune; CPI, check-point inhibitor; CSF-1R, colony-stimulating factor-1 receptor; EMA, European Medicines Agency; FDA, food and drug administration; irAEs, immune-related adverse events; NSCLC, non-small cell lung cancer; OVs, oncolytic viruses; PD1, programmed cell death-1; PD-L1, programmed cell death ligand 1; T-VEC, talimogene laherparepvec.

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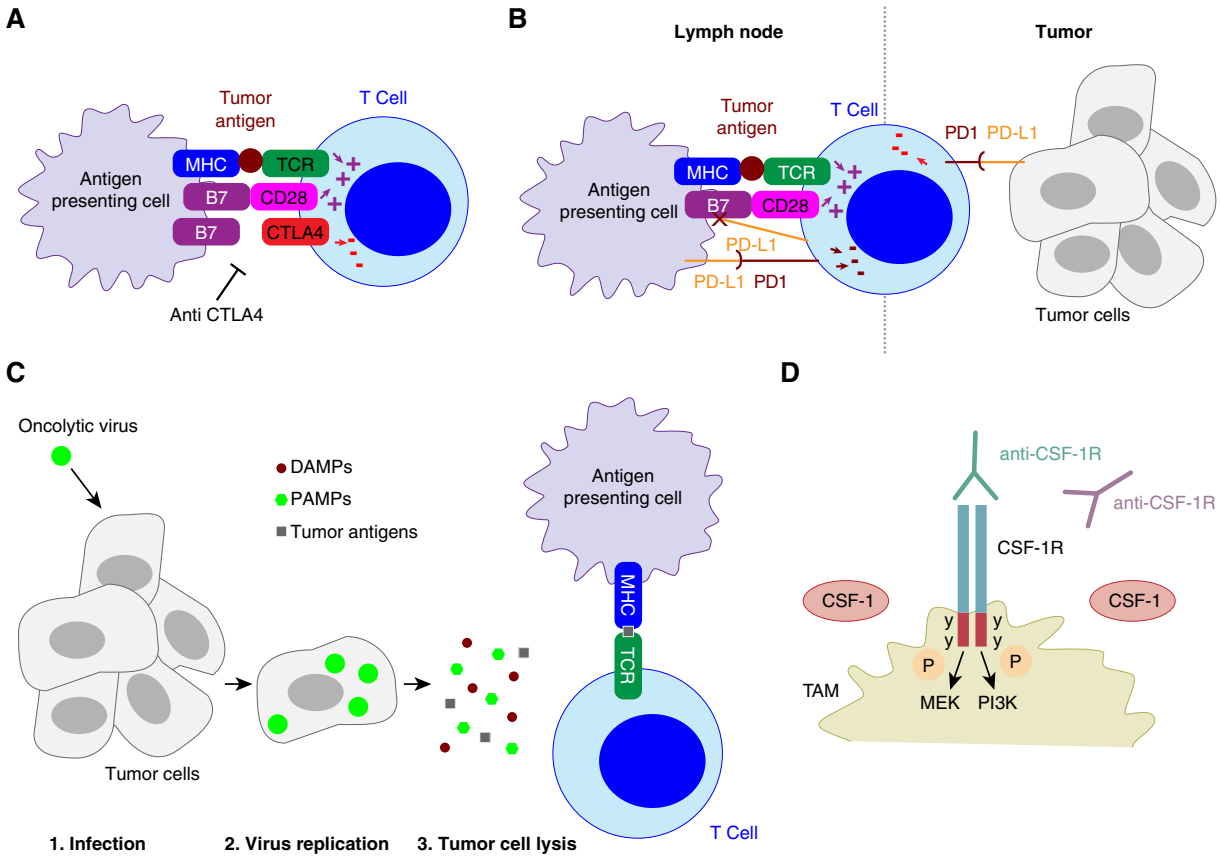

Fig. 1. Mechanisms of action of Immunotherapies. A: The activation of CD8 T-cell requires the tumor antigen presentation by a major histocompatibility complex (MHC) receptor in addition to the costimulatory signal (B7/CD28 interaction). Nevertheless, CTLA-4 upregulation after T-cell activation downregulates T-cell immune function. CTLA-4 antibodies are able to abrogate this immunotolerance and to reactivate the immune system against the tumor. B: Interaction of PD1 and its ligands PD-L1 occurs in every steps of the immune response (lymph node, tumor microenvironment). PD-1 is a negative regulator of the T-cell function. In the case of PD-1/PD-L1 interaction, tumor cells are able to escape the immunosurveillance. In the contrary, PD1 or PD-L1 antibodies can restore the anti-tumor immune response. C: Oncolytic viruses (Ovs) are able to invade and to replicate in tumor cells, leading to their lysis. The release of tumor antigens, DAMPs (damage-associated molecular patterns) and PAMPs (pathogen-associated molecular patterns) allows the recruitement of antigen presenting cells, able to present tumor antigens to T-cells. D: CSF-1R and its ligand CSF-1 regulate TAMs function, which are involved in tumorigenesis. Anti-CSF1 antibodies are able to block CSF-1R signalling, leading to an anti-tumor effect.

2. Checkpoint inhibitors

Although several well-described side effects, such as colitis with CTLA-4 inhibitors or cutaneous toxicities with CTLA-4 and anti PD1/PD-L1 inhibitors, have been described primarily due to their potential severity or frequency, the spectrum of irAEs for such molecules may affect all organs (Michot et al., 2016).

2.1. Safety profile

Several studies reported data related to the safety of immune checkpoint inhibitors (Table 1). A recent meta-analysis has summarized CTLA-4 inhibitors AEs occurrence in solid tumor patients (Bertrand, Kostine, Barnetche, Truchetet, & Schaeverbeke, 2015). Both ipilimumab and tremelimumab were evaluated. In addition to fatigue and decreased appetite, which are reported by 33–48% and 14–27% of patients, respectively, patients receiving CTLA-4 antibody treatment, exhibited specific irAE profiles, primarily skin (44%) and gastrointestinal (GI) (35%) side effects. Other systems were affected less frequently (<10%). GI side effects were primarily represented by diarrhea (33–51%), nausea (24–35%), and vomiting (12–24%). The most common skin AEs were papular rashes and/or pruritus, with alopecia and vitiligo reported more rarely. Endocrine AEs were primarily represented by hypophysitis (13%), followed by hypo−/hyperthyroiditis (<6%). High-grade toxicities (grade 3–4) occurred in 24% of patients with a related death rate of <0.5%. Despite a trend in an higher incidence of AEs with ipilimumab 10 mg/kg compared to ipilimumab 3 mg/kg (79% versus 61%), this difference did not reach the statistically significance. However, high grade AEs were significantly more frequent with ipilimumab 10 mg/kg than with ipilimumab 3 mg/kg: Risk-ratio = 3.1 [CI95%: 1.59–6.03], p = 0.0008 (Bertrand et al., 2015; Eggermont et al., 2015; Hodi et al., 2010; Mitchell, Kluger, Sznol, & Hartman, 2013; Ribas et al., 2013). The safety profile of PD1/PD-L1 antibodies appeared to be very similar, but the side effects were less frequent and were primarily low grade (Michot et al., 2016). Fatigue developed in 16–33% of patients. Interestingly, among skin toxicities, vitiligo was found in 5–10% of patients with melanoma but in no patient with NSCLC. PD1/PD-L1 irAEs were represented by the following manifestations: skin toxicities, mostly pruritus (6–21%) and rashes (4–15%), and endocrine side effects, including hypothyroiditis (4–9%), hyperthyroiditis (2–7%), and hypophysitis (<1%). Pneumonitis, nephritis, and colitis were uncommon (<2%) (Brahmer et al., 2015; Fehrenbacher et al., 2016; Garon et al., 2015; Ribas et al., 2015; Rizvi et al., 2015; Robert, Long, et al., 2015; Rosenberg et al., 2016; Weber, D'Angelo, et al., 2015). High-grade toxicities occurred in ~10% of patients (Borghaei et al., 2015; Motzer et al., 2015). There is no consistent data reporting a dose effect of PD1/PD-L1 antibodies on toxicities occurrence. In NSCLC patients, one study has suggested no statistically significant difference in AEs frequency between pembrolizumab at 10 mg/kg every 2 versus 3 weeks (Garon et al., 2015). A similar observation in melanoma patients treated