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Review

Rationally combining immunotherapies to improve efficacy of immune checkpoint blockade in solid tumors

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ABSTRACT

With the widespread application of immune checkpoint blocking antibodies (ICBs) for the treatment of advanced cancer, immunotherapy has proven to be capable of yielding unparalleled clinical results. However, despite the initial success of ICB-treatment, still a minority of patients experience durable responses to ICB therapy. A plethora of mechanisms underlie ICB resistance ranging from low immunogenicity, inadequate generation or recruitment of tumor-specific T cells or local suppression by stromal cells to acquired genetic alterations leading to immune escape. Increasing the response rates to ICBs requires insight into the mechanisms underlying resistance and the subsequent design of rational therapeutic combinations on a per patient basis. In this review, we aim to establish order into the mechanisms governing primary and secondary ICB resistance, offer therapeutic options to circumvent different modes of resistance and plea for a personalized medicine approach to maximize immunotherapeutic benefit for all cancer patients.

Contents

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1. Introduction

For many years, directing our immune system to target cancer was minimally effective in generating durable clinical responses. T-cell responses induced by often inferiorly formulated and designed vaccines were not powerful enough to overcome the many barriers posed by advanced solid tumors [1,2]. However, following the unprecedented results of 're-invigorating' T cells in a proportion of metastatic cancer patients by blocking immune inhibitory checkpoints, tumor immunotherapy has regained its position at the forefront of cancer treatment today [3]. To this date, the most studied and manipulated immune checkpoints on T cells are the receptors T lymphocyte associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1). Targeting CTLA-4 and the PD-1-PD-L1-axis with antagonistic antibodies has proven to be highly efficacious in a proportion of cancer patients (Fig. 1). The finding that a subgroup of patients has a pre-existing but dysfunctional anti-tumor immune response that can be therapeutically restored, prompts further investigation into what constitutes tumor immunity and precludes response to immunotherapy.

2. Current state of immune checkpoint blockade (ICB) in advanced cancer

Immune checkpoints are receptors expressed by T cells that upon ligation by their respective ligands regulate immune cell effector functions and proliferation thereby maintaining tolerance to self-antigens and ensure immune homeostasis [4,5]. Blocking inhibitory checkpoints using antagonistic antibodies may 'release the brakes' on T cells, including those cells specific for tumor antigens.

CTLA-4 is upregulated by T cells following recognition of cognate antigen by antigen presenting cells (APCs) in the lymph node [6]. The structure of CTLA-4 is nearly identical to the costimulatory receptor CD28 but interacts with much higher affinity for its ligands CD80/CD86 (B7-1/B7-2) expressed by the APC [7]. In contrast to CD28 stimulation, CTLA-4 has an inhibitory effect on effector T cells by causing cell cycle arrest [6,7]. Additionally, regulatory T cells (Tregs) constitutively express high levels of CTLA-4 on their cell surface, further facilitating their immune suppressive potential [8]. Antibodies directed towards CTLA-4 may therefore also act by decreasing Treg frequencies in blood and tumor via antibody dependent cytotoxicity (ADCC) [9,10].

Besides CTLA4, activated T cells express PD-1, and the coupling of PD-1 to programed cell death ligand 1 (PD-L1, also called B7-H1) or PD-L2 (B7-DC) restrains T-cell effector function and proliferation [11]. PD-L1 is expressed on tumor cells (constitutively due to oncogenic signaling or in response to interferons), myeloid cells including APCs, and PD-L2 is solely expressed by APCs [12]. It has recently been shown that both PD-L1 on host myeloid cells and on tumor cells is a prerequisite for anti-PD-1-therapy efficacy [13]. PD-1 was previously thought to attenuate T-cell receptor (TCR) -signaling but recent insights have firmly established the inhibitory role of PD-1 on downstream CD28-signalling in T-cells, further emphasizing the importance of proper (local) co-stimulation for T-cell function [14,15].

Thus far, four ICBs are FDA approved; anti-CTLA-4 (ipilimumab), anti-PD-1 (pembrolizumab and nivolumab) and anti-PD-L1 monoclonal antibodies (atezolizumab). Response rates vary between 11 and 40% depending on tumor type with PD-1 blockade yielding superior responses at a more favorable toxicity profile compared to CTLA-4 inhibition [16–20]. It has been suggested that the discrepancy in toxicities between ICBs can be explained by the

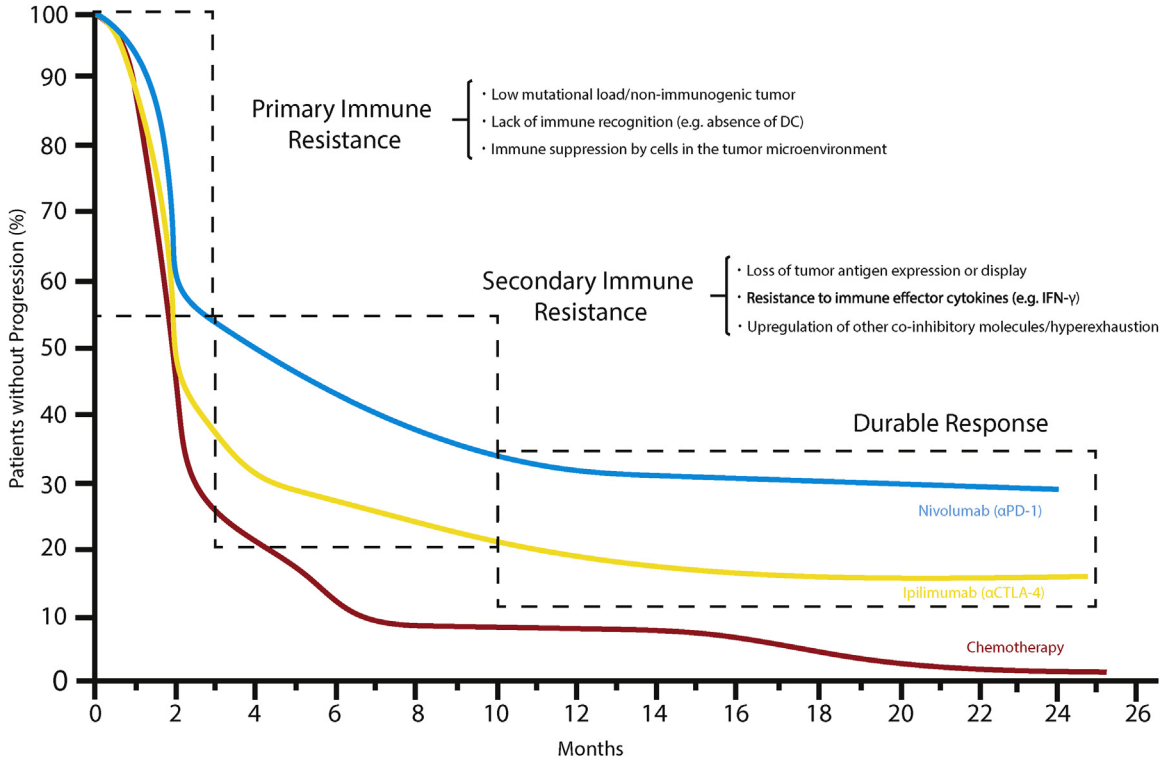

Fig. 1. Progression-free survival curves for chemotherapy, anti-PD-1- and anti-CTLA-4- checkpoint blockers; primary and secondary resistance to immune checkpoint blockade (ICB) therapy precludes patients from achieving durable responses and long-term survival. When patients do not respond to ICBs immediately following start of treatment they experience primary immune resistance. When patients do respond initially but relapse over time, secondary resistance to ICB-treatment has developed. PFS-curves have been derived from the following clinical trials investigating ICB-efficcacy in metastatic melanoma: Robert et al. NEJM 2011, Schachter et al. ASCO #9504 2016.