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Short Review

Immunotherapy targeting immune check-point(s) in brain metastases

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ABSTRACT

Immunotherapy with monoclonal antibodies (mAb) directed to different immune check-point(s) is showing a significant clinical impact in a growing number of human tumors of different histotype, both in terms of disease response and long-term survival patients. In this rapidly changing scenario, treatment of brain metastases remains an high unmeet medical need, and the efficacy of immunotherapy in these highly dismal clinical setting remains to be largely demonstrated. Nevertheless, up-coming observations are beginning to suggest a clinical potential of cancer immunotherapy also in brain metastases, regardless the underlying tumor histotype. These observations remain to be validated in larger clinical trials eventually designed also to address the efficacy of therapeutic mAb to immune check-point(s) within multimodality therapies for brain metastases. Noteworthy, the initial proofs of efficacy on immunotherapy in central nervous system metastases are already fostering clinical trials investigating its therapeutic potential also in primary brain tumors. We here review ongoing immunotherapeutic approaches to brain metastases and primary brain tumors, and the foreseeable strategies to overcome their main biologic hurdles and clinical challenges.

1. Introduction

Brain metastases pose a huge thread to treating physicians and, irrespective of treatment, the survival of cancer patients with intracranial disease remains extremely poor and frequently associates with quality of life impairing neurologic complications, making it one of the most daunting problems in oncology. Among solid tumors the highest incidence of brain metastases has been reported in lung (40%–50%), breast (15%–25%) and melanoma (40–50%) patients [1,2]. The median survival for subjects with untreated brain metastases is ~2 months but it can be extended to 12–15 months with a multi-disciplinary approach including surgery, radiotherapy and/or chemotherapy [3]. A very dismal prognosis characterizes also malignant primary brain tumors whose incidence accounted for 3.4 cases *per* 100,000 inhabitants in 2012 [4]; glioblastoma multiforme (GBM) being the most common (46%) and deadliest, with a 5-year survival rate of less than 5% [5]. Currently, there is no cure for GBM and the best first-line treatment still includes a combination of debulking surgery, chemotherapy and radiotherapy [6].

Due to the supposed role of the blood-brain barrier in preventing therapeutic agents from reaching the brain and to their worse prognosis, patients with brain metastases have been generally excluded from clinical trials designed to test the efficacy of novel therapeutic agents in the extracranial setting. A very similar situation has occurred also for the majority of clinical trials testing the efficacy of novel immunotherapeutic mAb targeting immune check-point(s). However, the success of this therapeutic approach in the extra-cranial disease has most recently fostered retrospective analyses and prospective clinical trials designed to explore its efficacy in brain metastases and, subsequently, in primary brain tumors. In this manuscript we review the most recent clinical evidence on the safety and efficacy of immune check-point(s) directed mAb in patients with brain metastases and primary central nervous system tumors.

2. Immune-checkpoints

The physiologic homeostasis of immune responses is controlled both by co-stimulatory (agonistic) and co-inhibitory (antagonistic) signals delivered by cell surface receptors belonging mainly to the immunoglobulin-like superfamily or to the tumor necrosis factor receptor superfamily [7]. Therefore, therapeutic mAb to agonistic or antagonistic immune check-points have been generated due to their potential to enhance anti-tumor immunity. Among co-stimulatory receptors in clinical development are OX40 and CD137,

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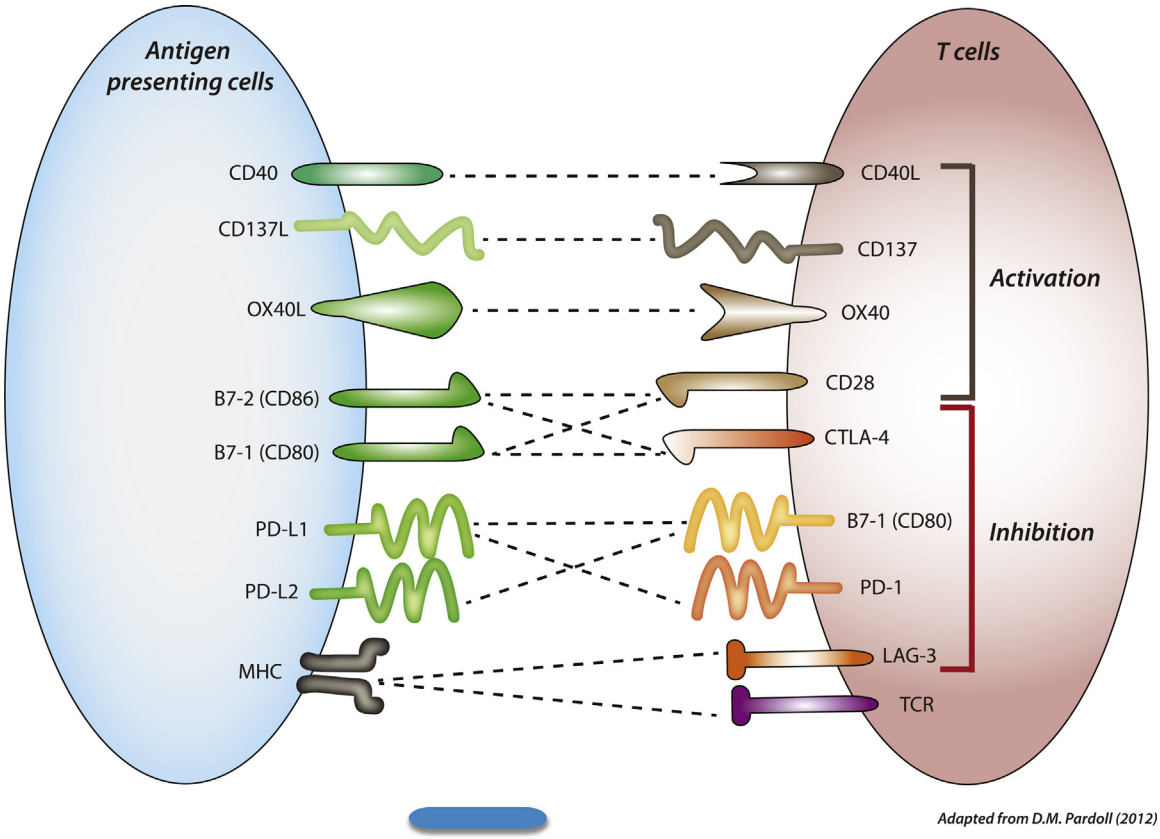

Fig. 1. T-cell Checkpoint and Co-stimulatory Pathways.
T cell response to antigen (which is mediated by peptide–major histocompatibility complex (MHC) molecule complexes that are recognized by the T cell receptor (TCR)) is regulated by various ligand–receptor interactions between T cells and antigen-presenting cells. Many of the ligands bind to multiple receptors, some of which deliver co-stimulatory signals and others inhibitory signals. Among co-stimulatory signals are the binding between: Cluster of differentiation 40 (CD40) and its ligand (CD40L); members of the tumor necrosis factor receptor family (CD137 and OX40) and their ligands (CD137L and OX40L); as well as the ligand between Cluster of differentiation 28 (CD28) with its receptors CD80 (B7.1) and CD86 (B7.2). Among inhibitory signals are the binding between cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) with its receptors CD80 (B7.1) and CD86 (B7.2); Programmed death- 1 (PD-1) and CD40 with programmed death-ligand 1 and 2 (PD-L1; PD-L2); lymphocyte activation gene 3 (LAG-3) with MHC class II.

while CTLA-4 and PD-1 are among the co-inhibitory ones [7] (Fig. 1). Treatment with mAb to CTLA-4 or to PD-1/PD-L1, as well as their combination has already shown significant clinical activity across a wide range of tumor types [8,9], being under clinical development in the majority of solid and hemopoietic malignancies.

3. Check-point monotherapy of brain metastases

3.1. Anti-CTLA-4

Initial clinical evidence providing proof of activity in brain metastases were generated with the anti-CTLA-4 mAb ipilimumab utilized as single agent in metastatic melanoma patients. A retrospective analysis of the phase II trial CheckMate CA189007 demonstrated that among the 115 treated subjects, 5 out of the 12 patients with stable brain metastases achieved a clinical benefit, with 3 of them surviving at 4 years [10,11]. Based on this observation, a subsequent phase II trial investigated the efficacy of ipilimumab in melanoma patients with asymptomatic (n = 51, cohort A) or symptomatic (n = 21, cohort B) brain metastases. Disease control rate (DCR) at 12 weeks was 26% and 10% in cohorts A and B, respectively. Median OS was 7 months (range 0.4–31 +) for cohort A and 4 months (0.5–25 +) for cohort B, while survival rates at 24 months were 26%, and 10%, respectively [12]. These very initial findings were subsequently confirmed in a large Italian expanded access program (EAP) with ipilimumab in which a 20% 1-year OS was observed in 146 melanoma patients with stable, asymptomatic, brain metastases [13].

3.2. Anti-PD-1

Providing support to the notion that patients with brain metastases can benefit from treatment with anti-check-point mAb, the activity of anti-PD-1 mAb monotherapy with nivolumab or pembrolizumab in subjects with intra-cranial disease was recently reported. The two-arm phase II trial of pembrolizumab in melanoma or Non-Small Cell Lung Cancer (NSCLC) patients with untreated brain metastases enrolled 32 subjects (18 melanoma and 18 NSCLC) with at least 1 asymptomatic, untreated or progressive brain lesion with a diameter ranging from 5 to 20 mm. Durable intracranial objective responses were achieved in 4 and 6 melanoma and NSCLC patients, respectively [14].

A more recent retrospective analysis of 66 melanoma patients with brain metastases treated with nivolumab or pembrolizumab reported an intracranial overall response rate (ORR) and a DCR in 21% and 56% subjects, respectively. The median OS was 9.9 months (95% CI 6.93–17.74). Patients with symptomatic brain metastases had a shorter progression free survival (PFS) compared to the asymptomatic ones (2.7 *vs* 7.4 months, p = 0.035), and a shorter OS (5.7 *vs* 13.0 months, $p = 0.068$) [15].