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Immune Checkpoint Blockade Therapy: Merits and Demerits

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Abstract

The up regulation of anti-tumor responses by immune-checkpoint blockade is a new approach for the treatment of advanced solid malignant tumors. There are some demerits to this therapy that require an evaluation of eligibility and efficacy, balanced against adverse effects and cost. Treatment for patients without immune checkpoint receptors or ligands remains an issue of concern. The cost of this therapy is huge and is further increased when treatment is required for adverse effects. The appropriate use of immune checkpoint therapy requires careful consideration.

Keywords: Immune checkpoint; PD-1; PD-L1 (CD274); PD-L2 (CD273); Melanoma; Cost

Introduction

The up regulation of anti-tumor responses by immune-checkpoint blockade is a new approach for the treatment of advanced solid malignant tumors. The checkpoints are important immune interactions between T cells and tumor cells. One key molecule in these immune interactions is programmed cell-death 1 (PD-1). There are two ligands of PD-1 and PD-L2. The blockade of PD-1 and PD-L1 binding using these antibodies upregulates the anti-tumor response. There are some demerits to this therapy that require an evaluation of eligibility and efficacy, balanced against adverse effects and cost. In cases with a low positive or negative rate of these receptors or ligands, immune checkpoint therapy is not effective.

Treatment for patients without immune checkpoint receptors or ligands remains an issue of concern. The cost of this therapy is huge and is further increased when treatment is required for adverse effects. The appropriate use of immune checkpoint therapy requires careful consideration.

Merits of Immune Checkpoint Therapy

Immune checkpoint blockade therapy

Immune checkpoint blockade therapy using immune checkpoint-targeted antibodies is a new treatment option for advanced malignant melanoma, and this therapy is a new approaches in solid other malignant tumors.

In this treatment modality, the checkpoints are important immune interactions between T cells and antigen-presenting cells (APCs) or tumor cells (Figure 1). There are two key molecules in these immune interactions: programmed cell-death 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) expressed on T cells [1].

PD-1 is well-known as a T cell inhibitory receptor (antitumor immunity) expressed on activated T and B cells [2-5]. PD-1 belongs to the CD28 family [3,4], and is a marker of T cell exhaustion [6]. The functions of PD-1 in the immune response stop on-going immune activity in tissues [7]. There are two ligands of PD-1: PD-L1 (B7-H1, CD274) [8-11] and PD-L2 (B7-DC, CD273) [9-11]. These ligands are induced in inflammatory tissues [12]. Certain types of solid tumors and APCs express PD-L1 and PD-L2 on the cell surface [11-13]. PD-L1 expressed on tumor cells is a key ligand in evading anti-tumor immunity [13], and can be induced by tumor-infiltrating CD4+ and CD8+ T lymphocytes [14-16]. When PD-1 on T cells binds with PD-L1 on tumor cells, these T cells receive signals of inhibited T cell immunity against tumors [17,18], and tumor cells then grow and proliferate (Figure 1) [6]. The role of PD-L2 is not clear, but it is known that PD-L2 is restricted to and expressed on macrophages and dendritic cells [19,20]. PD-L1 and PD-L2 expressed on APCs induce T cell anergy or apoptosis via PD-1 on T cells [21]. The ligands of PD on tumor cells regulate adaptive Tregs, resulting in tumor-induced immune suppression [22]. Many PD-1 molecules are found on circulating T cells and tumor-infiltrating T cells in melanoma patients [23]. The blockade of PD-1 and PD-L1 binding using these antibodies up regulates the anti-tumor response (PD-L1 and PD-L2 reactivate the anti-tumor immune response (Figure 2) [18]), enhances the functional capacity of cytotoxic T cells against human melanoma antigen [24], decreases tumors, and prolongs patient survival.

The agents of immune checkpoint therapy

Antibodies against PD-1 include nivolumab (BMS-936558, MDX-1106 and ONO-4538) and pembrolizumab (MK-3475): Nivolumab is an IgG4 monoclonal antibody that binds the PD-1 receptor to block its interaction with PD-L1 [23,25,26]. PD-L1 expression on tumor cells is a required biomarker of an effective response to nivolumab therapy [26]. Cases with PD-L1-negative tumors show no objective response [26,27]. Previous reports indicate that PD-L1 is expressed in 38-50% of melanomas (including metastatic melanoma) [28-31] and these PD-L1-positive cases all exhibited an objective response.

Nivolumab was approved in July 2014 in Japan and in December 2014 in the United States for unresectable or metastatic melanoma cases, and has already shown impressive and interesting results in clinical trials [2,27,32,33]. Nivolumab therapy is thus expected to make

a substantial contribution to the treatment of advanced malignant melanoma.

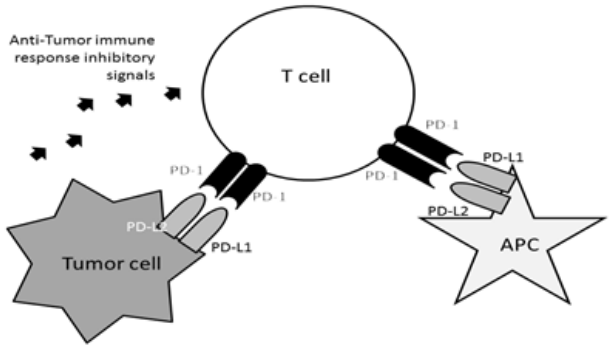

Figure 1: Interaction between T cells and tumor cells or APCs.

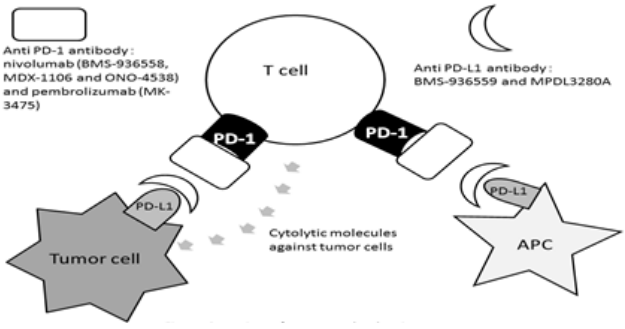

Figure 2: Action of immune checkpoint agents.

Pembrolizumab is an IgG4 monoclonal antibody that binds to PD-1, resulting in T cell immunity against tumors. This agent has been approved by the Food and Drug Administration (FDA) in the US [26]. Iannone [34] reported that pembrolizumab achieved a high objective response rate (47%) in cases of advanced melanoma. In phase 1 trials using MK-3475 in 135 advanced melanoma patients, the overall objective response was 38%, and a 52% objective response was shown when using the maximum dose [35].

Antibodies against the ligand of PD-1 include BMS-936559 and MPDL3280A: BMS-936559 is an IgG4 monoclonal antibody that inhibits binding of PD-L1 to PD-1 and CD80 [20,36]. A phase 1 trial using this agent showed a 17% (9 of 52 melanoma patients) rate of complete or partial response [36].

MPDL3280A is a monoclonal antibody to PD-L1 that has achieved an objective response in clinical trials [35]. The objective response in advanced melanoma cases using this agent was reported to be 29% (10/35) at the 2013 annual conference of the American Society of Clinical Oncology [35].

Antibody against CTLA-4: Ipilimumab is an IgG1 monoclonal antibody that binds to CTLA-4. CTLA-4 reduces the T cell response against self-antigens and prevents autoimmunity [3]. This antibody prevents cytotoxic T cell down regulation [37]. Clinical trials using ipilimumab in melanoma cases have shown improved survival rates [38], which have been estimated to be 49-60% [39,40].

Demerits of Immune Checkpoint Therapy

In cases with a low positive or negative rate of these receptors or ligands, immune checkpoint therapy is not effective. It is important to study positive rates of immune checkpoint molecules before therapy using these agents, while keeping in mind that treatment for patients without immune checkpoint receptors or ligands remains an issue of concern.

The most frequent adverse effects of immune checkpoint therapy are skin rashes, followed by gastrointestinal symptoms; other adverse effects include endocrine, liver, pulmonary and general symptoms [18,20,37]. Select adverse events in clinical trials occurred in 40-60% of patients, and 3-20% of these cases were grade 3 or 4 [37].

Combination therapy using immune checkpoint agents could produce more effective results, but adverse effects are more common than when using a single agent [41]. Using a concurrent regimen, Jedd [41] reported grade 3 or 4 adverse effects in 53% of patients. The rates of adverse effects when using only ipilimumab or nivolumab are reported to be 20% and 15%, respectively [38]. Kourie [42] reports that combination therapy using many checkpoint inhibitors was associated with high response rates (>50%) in melanomas, but that 30% of patients had to discontinue combination therapy using nivolumab and ipilimumab because of high toxicity.

In the US, the average annual number of adults treated for skin cancer and the annual cost for skin cancer increased from 2002 to 2011 [43], and these numbers are likewise increasing in other countries as well. The costs of immune checkpoint therapy are huge, and those of combination therapies are even higher. Therefore, eligibility for this therapy should be determined based on disease severity, and the kinds and rates of positive immune checkpoints. The cost of using just one immune checkpoint therapy, nivolumab, is at least a few million yen per month in Japan, and almost all costs (about 97-98%) are covered by insurance for high medical expenses and by the national budget. Therefore, both in Japan and other countries, national health budgets and medical insurance companies could go bankrupt if all candidate cases are treated with immune checkpoint therapies. Moreover, the cost of immune checkpoint therapies is further increased when treatment is required for adverse effects.

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