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Review article / Обзорная статья

PD-L1 as a Potential Target in Cancer Therapy (Review)

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Abstract

Introduction. Cancer is one of the most serious and common diseases with a high level of mortality. Due to this reason the searching of new directions and methods of cancer treatment is becoming more and more important with each passing year. Significant advances in cancer immunotherapy have been reached over the past few decades. Moreover, an inhibition of the interaction between the programmed cell death receptor (PD-1) and its ligand (PD-L1), is sure to be perspective direction of the immuno-oncological therapy development.

Text. PD-1/PD-L1 interaction plays a pivotal role in negative regulation of immune system, that protects host's cells and tissues from the excessive immune response. However, it is also used by tumor cells to avoid the host's immune system. The discovery of this mechanism led to the development of inhibiting PD-1 or PD-L1 agents that enhance anti-tumor immunity. Meanwhile, anti-PD-L1 agents provide less toxicity in comparison with anti-PD-1 agents. FDA currently approved Atesolizumab, Durvalumab, and Avelumab PD-L1 inhibitors for cancer treatment. These agents demonstrated effective response during the clinical trials, however, they are used for a limited number of oncological diseases. In addition, BMS-936559 is a promising agent that had passed the first stage of the clinical trials. Nevertheless, immunotherapy involving PD-L1 inhibitors is closely related to a vast number of severe side effects including immune-mediated effects caused by the inhibition of PD-L1 ligands located on healthy cells. In these terms, the development of new agents deprived of these disadvantages is the reason for further studies.

Conclusion. Immunotherapy in cancer uncovers new perspectives in treatment of refractory to standard therapies forms of cancer. And the development of new and improvement of existing PD-L1 blocking agents are of great importance in fighting against tumoral diseases.

Keywords: PD-L1 inhibitor, immune checkpoint blockade, cancer immunotherapy, atezolizumab, durvalumab, avelumab, monoclonal antibody

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PD-L1 как потенциальная мишень в противораковой терапии (обзор)

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Резюме

Введение. Рак является одним из самых тяжелых и распространенных заболеваний с высокой вероятностью летального исхода, поэтому поиск новых направлений и способов лечения раковых заболеваний с каждым годом приобретает все большую актуальность. За последние несколько десятков лет были достигнуты значительные успехи в иммунотерапии рака. При этом перспективным направлением иммуноонкологической терапии является блокирование взаимодействия рецептора программируемой клеточной смерти (PD-1) с его лигандом (PD-L1).

Текст. Взаимодействие PD-1/PD-L1 играет важную роль в отрицательной регуляции иммунной системы, защищая клетки и ткани организма хозяина от чрезмерного иммунного ответа. Однако данный механизм также используется опухолевыми клетками для подавления иммунного ответа организма хозяина. Обнаружение этого механизма положило начало разработке лекарственных препаратов, ингибирующих PD-1 или PD-L1, целью которых является усиление противоопухолевого иммунитета. При этом анти-PD-L1-препараты обладают потенциально меньшей токсичностью по сравнению с анти-PD-1. В настоящее время для применения FDA (Food and Drug Administration, США) одобрены ингибиторы PD-L1 Атезолизумаб, Дурвалумаб и Авелумаб. Данные лекарственные средства обладают достаточной эффективностью, подтвержденной клиническими исследованиями, однако применяются для очень ограниченного числа онкологических заболеваний. Потенциально перспективным лекарственным препаратом является BMS-936559, который прошел только первую стадию клинических испытаний. Однако иммуноонкологическая терапия ингибиторами PD-L1 сопряжена с возникновением большого числа тяжелых побочных эффектов, в том числе иммуноопосредованных, которые возникают из-за блокирования лигандов PD-L1, находящихся на здоровых клетках. Это стимулирует проведение дальнейших исследований, направленных на разработку новых лекарственных препаратов, лишенных отмеченных недостатков.

Заключение. Иммунотерапия злокачественных новообразований несет в себе огромный потенциал и открывает новые горизонты в лечении форм рака, рефрактерных к стандартным методам лечения. При этом разработка новых и усовершенствование существующих лекарственных препаратов-ингибиторов PD-L1 являются перспективными направлениями, определяющими траекторию борьбы с опухолевыми заболеваниями.

Ключевые слова: PD-L1-ингибитор, блокировка контрольных точек иммунитета, иммунотерапия рака, авелумаб, дурвалумаб, атезолизумаб, моноклональные антитела

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INTRODUCTION

Cancer diseases still take the leading positions in the number of lethal cases both in Russia and worldwide. Therefore the development and improvement of methods for cancer therapy is an up-to-date problem and the priority trend of studies in many countries.

During the last decades, numerous immunotherapeutic approaches to cancer therapy were developed and evaluated. And, though the results of these numerous early efforts were disappointing, the ability to induce long remissions of large tumors with high doses of interleukin-2 (HD-IL-2), interferon α and vaccines nevertheless provided evidence of high immunotherapy potential [1, 2]. Further studies have provided a clearer understanding of the facts limiting antineoplastic immune response that lead to the development of various drug agents which target immunostimulating and immunosuppressor pathways. One of the key drug targets is the ligand of programmed cell death protein-receptor PD-L1 involved in the mechanism of the immunosuppression induced by a tumor.

This review contains the detailed information on the drugs targeting PD-L1 ligand which are used nowadays.

General characteristics of PD-1/PD-L1 interaction

PD-1 (programmed cell death receptor) represents a transmembrane protein from immunoglobulins family. PD-1 receptor, along with CTLA4 receptor, plays an important role in negative regulation of the immune system inhibiting activity of cytotoxic T-lymphocytes that prevents autoimmune reaction and cells damages in inflammations [3]. It consists of the extracellular N-end IgV-like domain, the transmembrane domain and the cytoplasmatic end involved to inhibitory signaling [4]. PD-1 is expressed on the activated immune cells including CD4+ T-cells, CD8+ T-cells, B-cells, NK cells, monocytes, dendrites, macrophages, as well as, tumor infiltrating cells [5]. Moreover, PD-1 is selectively activated in T-cells in response to constant antigen exposure. Thus, PD-1 expression in T-cells is one of the markers of T-lymphocyte depletion [6].

There are two known ligands of PD-1 receptor – PD-L1 (B7- H1) and PD-L2 (B7-DC) belonging to B7 family. PD-L1 is expressed in various hematopoietic, as well as, endothelial and epithelial cells [7]. PD-L2 also expressed in a limited way, mainly on activated macrophages and dendrites [8]. However PD-L1 may be also expressed on tumor cells and tumor infiltrating cells of the immune system – lymphoid and myeloid, and stromal cells mediating tumor integration [9]. Numerous cases of PD-L1 expression in different cancer types including melanoma, multiple myeloma, leukemia, glioblastoma and gastric, renal, bladder, breast and lung cancer are described [10–12]. When bound to PD-L1 ligand in a tumor cell with T-lymphocyte PD-1 receptor, T-cell cytotoxic activity is suppressed by inhibition of proliferation of T-lymphocytes and cytokine products. As well, the apoptosis of tumor infiltrating T-cells is induced [13]. Thus, PD-L1/PD-1 interaction plays an important role in the mechanism of tumor evasion from the immune response. Therefore, the blockage of this interaction promotes the termination of the PD-L1/PD-1 mediated suppression of the immune response and causes reactivation of antineoplastic immunity that in fact the challenge for cancer immunotherapy.

Drugs – PD-L1 inhibitors

Cancer immunotherapies gain more physicians' confidence as new treatment methods for malignant neoplasms. Inhibitors of PD-1/PD-L1-pathways take the special position in cancer immunotherapy as they appear effective in treatment of cancer diseases not susceptible to standard treatment methods. It is suggested that the selection as a PD-L1 ligand target may be accompanied with lower toxicity, partially by selective modulation of the immune response in a tumor microenvironment that provides a great interest to its selection as a target for drug products [14].

Nowadays, drugs – PD-L1 inhibitors Atezolizumab, Durvalumab and Avelumab (table 1) are recommended

for systemic therapy of locally spreading and metastatic cancer diseases by the European Society of Medical Oncology.

Atezolizumab

Atezolizumab – humanized monoclonal antibodies, immunoglobulins G (IgG1) with a modified Fc-fragment. Atezolizumab binds directly with PD-L1 ligand and blocks its interaction with PD-1 receptor [15].

The drug is approved for treatment of patients with locally spreading and metastatic urothelial carcinoma expressing PD-L1 ≥5 % on immunocompetent cells who fail Cisplatin therapy [16]. It is indicated when any platinum-containing chemotherapy is impossible, irrespective of PD-L1 expression level. Atezolizumab is indicated to patients with disease progression during or after of any platinum-containing chemotherapy within 12 months after neoadjuvant or adjuvant chemotherapy [16]. The efficacy of atezolizumab is proven in clinical trials in which the objective response rate was 23 % and 25 %, respectively [17, 18].

Atezolizumab is used in combined treatment of non-small cell lung cancer with Bevacizumab, Paclitaxel, Carboplatin and Nab-palitaxel in the first-line therapy and in monotherapy of locally spreading or metastatic non-small cell lung cancer in adult patients [16]. Combined with chemotherapy, Atezolizumab considerably reduces the risk. of disease progression and mortality compared to chemotherapy alone [19].

In 2019, the FDA approved Atezolizumab in combined therapy of an inoperable locally spreading or metastatic triple-negative breast cancer in the first-line therapy combined with Nab-paclitaxel with PD-L1 expression ≥1 % on immunocompetent tumor infiltrating cells [16]. The clinical trials have shown that Atezolizumab in combination with Nab-paclitaxel reduces the risk of disease progression or death, and also increases the total survival of patients almost for 9.5 months compared to Nab-paclitaxel monotherapy [20].

The clinical trials aimed to determine Atezolizumab efficacy in renal cancer [21] are ongoing.

Durvalumab

Durvalumab (Imfinzi®) represents human monoclonal antibodies – immunoglobulins G (IgG1) which block biding of PD-L1 ligand with PD-1 receptor allowing T-lymphocytes to differentiate and destroy tumor cells. At the same time, PD-1 interaction with PD-L2 is not affected [22].

The drug is approved by the FDA for treatment of adult patients with locally spreading and metastatic urothelial carcinoma observed during platinum-containing chemotherapy and progressing after the treatment [23].

Avelumab

Avelumab – fully human monoclonal IgG1 antibodies which, unlike other drugs, not only inhibit PD-1/PD-L1 interaction but also influence antibody-dependent cell-mediated cytotoxicity that causes lysis of tumor cells [27].

Avelumab administration as a drug for treatment of Merkel-cell carcinoma of adult patients and children above 12 years is based on the clinical trials, whose objective response rate was 29.5 %, with the response lasting from 2.8 to 14.6 months (the median was not established) [28, 29]. The drug is effective and considerably increases life expectancy of patients with the urothelial carcinoma progressing during or after platinum-containing chemotherapy and in combined therapy with Axitinib for patients with progressive renal cancer [30, 31].

The promising trend for avelumab is treatment of breast cancer and relapsing, and refractory ovarian cancer [32–34].

BMS-936559

Product BMS-936559 by Bristol-Myers Squibb represents fully human antibodies, IgG4 immunoglobulins with high affinity to PD-L1 molecule. Nowadays, only the first stage of the drug clinical trials has been carried out on patients with melanoma, renal cancer and non-small cell cancer [35, 36]. BMS-936559 has a sufficient potential to be among other drugs inhibiting immunity check-

Таблица 1. Лекарственные препараты-ингибиторы PD-L1

Medicinal product (INN)	Trade name	Manufacturing company	Application
Atezolizumab (MPDL3280A)	Tecentrik®	Roche	Non-small cell lung cancer, urothelial carcinoma, triple negative breast cancer
Durvalumab (MEDI4736)	Imfinzi®	AstraZeneca	Locally advanced and metastatic urothelial carcinoma, non-small cell lung cancer
Avelumab (MSB0010718C)	Bavencio®	Merck KgaA и Pfizer	Merkel carcinoma, kidney cancer, urothelial carcinoma

points however the manufacturer did not inform about the intentions to carry out further clinical trials of the drug product.

Development prospectives of anti-PD-L1 cancer immunotherapies

Despite prospectives of cancer immunotherapies – immunity checkpoint inhibitors, their use is limited due to some difficulties. First of all, the programmed cell death receptor ligand expresses not only on tumor cells but also on healthy host cells that is a protective body reaction from the excessive damage caused by T-cells inflammation. In this context, cancer immunotherapy shall be specifically targeted on tumor sites but not on system activation of the immune system. This selectivity may be achieved by identification of the immunomodulatory targets being directly within a tumor. The differentiated approach lies in addition of components targeting a tumor to systemic immune response activators that will limit location of their action [37].

Other important feature of cancer immunotherapies is efficacy of drugs of this type proven for rather few cancer types whereas long response is not observed in most epithelial malignancies.

Finally, immunotherapy is closely related to a wide range of adverse effects such as fatigue, itching, rash, nausea, type 1 diabetes, pneumonia, etc. [38]. Checkpoint inhibitors can also cause immuno-mediated adverse effects in almost in any body system. Most of them are reversible, except for endocrine effects, and lethal outcomes occur rarely. The clinical trials have shown that 21 % of cancer patients receiving immunity checkpoint inhibitors had immuno-mediated adverse effects, one lethal outcome was reported among 28 patients due to pneumonitis and colitis [39]. Moreover, monoclonal antibodies may cause drug immunogenicity which, in its turn, may also cause adverse reactions and reduce clinical efficacy [40].

The decrease of adverse effects related to the comprehensive investigation of anti-PD-L1 drug effects on body functions is one of the greatest study priorities.

CONCLUSION

Cancer immunotherapy opens new opportunities in treatment of malignant neoplasms. Investigation of the mechanism of PD-1/PD-L1 interaction, as well as, the development of new and improvement of the existing anti-PD-L1-drugs has a great potential for treatment of tumors refractory to standard therapies.

The FDA approved three drugs of this type: Atezolizumab, Avelumab and Durvalmab which has allowed to increase treatment efficacy for patients with multiple disease relapses.

Despite the fact that efficacy of anti-PD-L1-therapy is confirmed with clinical trials on numerous cancer types, study efficacy of drugs in other cancer diseases is still the challenging trend for investigations that represents the prospective of their expanded use. The development of new methods for targeted delivery of the existing drugs, as well as investigation and search of methods for decrease of adverse effects are equally important fields.

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