Libyan International Medical University

Faculty of Basic Medical Science

Using of checkpoint inhibitors as a treatment for melanoma

Khadija Netfa

Supervised by: Dr.Rashad Shawgi

Assisted by: Raihan Obydi

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Abstract

Immune checkpoint blockade has used as a treatment of patients with advanced melanoma and many other cancers. Blockade of inhibitory receptors, cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death receptor 1 (PD-1) that enhances T-cell-mediated antitumor immune responses leading to improved immune responses, based on their studies and mechanism of action in the treatment of metastatic melanoma.

Introduction

Immune checkpoint inhibitors are drugs that help the immune system to release "brakes" of inhibitory receptors expressed on the surface of activated T-cells, cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death receptor 1 (PD-1) that enhances T-cell-mediated antitumor immune responses leading to improved immune responses. Ipilimumab and Nivolumab are examples of immune checkpoint inhibitors, where ipilimumab targets CTLA-4 and nivolumab targets PD-1/PD-L1.

The activation and control of T-cell responses: interaction of the T-cell receptor (TCR) and accessory molecule (CD4 or CD8) on the T-cell with peptide-MHC on the surface of an antigen-presenting cell (APC) together with co-stimulatory molecule CD28 on the T-cell interacting with B7 family ligands CD80 and CD86 on APCs results in T-cell activation and CD28 promotes enhanced proliferation, IL-2 production, and T-cell survival.

Immune checkpoints CTLA-4 and PD-1/PD-L1 are expressed on T-cells after activation and serve to control the mechanism to turn off T-cell responses and prevent destructive inflammation by its co-inhibitory signals. Treg cells also suppress T-cell functions. CTLA-4 and PD-1 are targets of immunotherapeutics in melanoma. Blockade of these immune checkpoints augments antitumor T-cell responses[1].

Aims of the Study

To discuss the benefit of checkpoint inhibitors in treatment of melanoma by discussing their mechanism of action and its studies.

Methods:

Based on several clinical studies of ipilimumab, nivolumab and other treatments for metastatic melanoma from data in 2017[1].

Results:

Based on results in studies of ipilimumab, nivolumab and other treatments for metastatic melanoma by comparing the overall survival rate, median overall survival and response rate[1].

Table (1)[1]: Ipilimumab clinical data in advanced melanoma treatment

Study arms	Number	Previous treatment	1-Year overall survival (%)	Median overall survival	response rate
Ipilimumab	131	Yes	45.6%	10.1 months	10.9%
Ipilimumab + Glycoprotein 100 (gp100)	380	Yes	43.6%	10 months	5.7%
gp100peptide vaccine	132	Yes	25.3%	6.4 months	1.5%
Ipilimumab+Dacarbazine	250	No	47.3%	11.2 months	15.2%
Placebo + Dacarbazine	252	No	36.3%	9.1 months	10.3%

Table (2)[1]: PD-1 Blockade Clinical Data in the First-Line Treatment of Advanced Melanoma

Study arms	Number	1-Year overall survival (%)	Median overall survival	response rate
Nivolumab vs Dacarbazine	206,205	72.9%,42.1%	5.1 months, 2.2 months	40%,13.9%
Nivolumab+Ipilimumab	314	Not available	11.5 months	57.6%

Nivolumab	316	Not available	6.9 months	43.7%
Ipilimumab	315	Not available	2.9 months	19%

Discussion:

1.1- CTLA-4 blockade in the treatment of melanoma:

Ipilimumab is a monoclonal antibody of the IgG1 isotype that binds CTLA-4, preventing it from interacting with its ligands. The mechanism of action of ipilimumab is enhancing T-cell-mediated antitumor immunity through blocking an inhibitory receptor on effector T-cells and depleting treg cells[1].

Based on results in early clinical studies of ipilimumab for metastatic melanoma, ipilimumab was advanced into phase III trials. In the first phase III study, previously treated patients with unresectable stage III or stage IV melanoma were treated with ipilimumab alone, ipilimumab with a glycoprotein 100 (gp100) melanoma specific peptide vaccine, or gp100 alone. This study demonstrated improved overall survival in patients receiving ipilimumab (10.1 months for ipilimumab alone and 10.0 months for ipilimumab and gp100, compared with 6.4 months for gp100 alone) and the overall response rate, including complete and partial responses, was 10.9% for ipilimumab, 5.7% for ipilimumab and gp100, and 1.5% for gp100 alone[2], that led to the FDA approval of ipilimumab for patients with late stage, unresectable melanoma[1].

A subsequent study demonstrated a median overall survival benefit of ipilimumab plus dacarbazine compared to placebo and dacarbazine (11.2 months vs. 9.1 months) in previously untreated metastatic melanoma patients. Overall response rates were 15.2% for ipilimumab and dacarbazine versus 10.3% for placebo and dacarbazine[3].

Another study compared between tremelimumab vs dacarbazine and ipilimumab, where they found that tremelimumab has a less overall survival than others[4].

1.2- PD-1 blockade in the treatment of melanoma:

There are several PD-1-blocking antibodies have been developed, including nivolumab and pembrolizumab. Nivolumab is a human monoclonal antibody of the IgG4 isotype that binds to PD-1, preventing it from interacting with its ligands[1].

In patients were treated with either nivolumab or dacarbazine, and the nivolumab group demonstrated improved efficacy in terms of 1-year overall survival (72.9% vs. 42.1%), median overall survival (5.1 months vs. 2.2 months), and the response rate (40.0% vs. 13.9%) [1].

In previously untreated melanoma patients compared nivolumab and ipilimumab combination therapy, nivolumab alone, and ipilimumab alone, the median overall survival was 11.5 months, 6.9 months, and 2.9 months, respectively. The response rate was 57.6, 43.7, and 19.0%, respectively. The median overall survival and the response rate were improved in both the nivolumab and ipilimumab combination and the nivolumab alone groups compared with the ipilimumab group[5].

Conclusion:

Immune checkpoint inhibitors have a role in treatment of melanoma and many other cancers by blocking antibodies to CTLA-4 and PD-1 to enhances T-cell-mediated antitumor immune responses, including ipilimumab and nivolumab were they have a high response rate in patients with last stages of melanoma comparing with other treatments.

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