

Is Cancer Immunotherapy More Hype Than Hope?

Apakah Imunoterapi Kanker Sebuah Harapan Atau Hanya Sebuah Sensasi?

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Abstract

The immunosurveillance system in the human body can detect and eradicate abnormal cells. However, cancer cells can avoid immune destruction by exploiting the immunosuppression system. Extensive research has been done to find therapeutic agents that could reverse this condition. Novel drugs called checkpoint inhibitors have been developed and showed a promising result. Besides, "living" drug, an engineered T-cells which can accurately target cancer cells, has increased public attention in immunotherapy. These immunotherapies might bring a new era of cancer management, a highly effective and specific treatment with fewer adverse effects.

Keywords: *Immunosurveillance; T-Cell; Therapeutic agents; Immunotherapies*

Abstrak

Sistem pengawasan atau monitoring kekebalan tubuh manusia berfungsi mendeteksi dan menghancurkan sel yang abnormal. Namun menariknya, sel kanker mempunyai kemampuan untuk menghindari dan memanipulasi deteksi sistem kekebalan tubuh sehingga mencegah kerusakan dirinya. Banyak sekali penelitian dilakukan untuk menjawab fenomena tersebut. Disisi lain, penelitian yang ekstensif juga telah dilakukan untuk menemukan agen terapeutik yang dapat menjawab fenomena tersebut. Obat-obatan inhibitor telah dikembangkan dan menunjukkan hasil yang menjanjikan. Selain itu, obat "hidup", sel T yang direkayasa yang secara akurat dapat menargetkan sel kanker, telah meningkatkan perhatian publik dalam bidang imunoterapi. Imunoterapi ini mungkin membawa era baru pengelolaan kanker, dengan keunggulan pendekatan pengobatan yang sangat efektif dan spesifik dengan efek samping yang lebih sedikit

Kata Kunci: Sistem pengawasan kekebalan tubuh manusia; Sel T; Zat terapeutik; Imunoterapi

Introduction

The human body has developed an immune system that can recognize and eradicate cancer cells. Accumulation of mutation on cancer cell genes will produce abnormal proteins, which may be considered as foreign antigens by the immune cells.¹ According to Chen and Mellmann², the anti-tumor immune response is a cycle that can be separated into seven steps

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(Figure 1). The cycle begins with the release of antigens by the dead cancer cells which will cause T-lymphocyte activation. The activated T-lymphocytes then enter the bloodstream and migrate to the site of cancer cells. Once reached the site of action, the T-lymphocyte secretes perforin and granzyme which will kill the cancer cells. The lysis of the cancer cells results in further release of antigens and the cycle of immune response starts again (Figure 1).

However, as stated by Hanahan and Weinberg³, one of the hallmarks of cancer is the avoidance of immune destruction. Cancer cells achieve this by exploiting the immunosuppression system which in normal physiologic condition functions to prevent prolonged inflammation and autoimmunity.⁴ According to Mellman, Coukus, and Dranoff, mediators such as TGF- β , adenosine & VEGF-A are secreted by cancer cells to inhibit cytotoxic T-lymphocyte penetration and activation.⁵ These substances also stimulate T-regulatory lymphocyte expansion in the tumor microenvironment, which will directly suppress CD8 and CD4 lymphocyte function. The Major Histocompatibility Complex (MHC) class 1 down-regulation in melanoma cells is also one of the mechanisms to evade detection from lymphocyte and promote the oncogenic potential of cancer cells.⁶ Furthermore, Zou and Chen state that some cancer cells upregulate the expression of PD-1 ligand. This ligand will bind to PD-1 on T-lymphocyte and then suppress T-lymphocyte responses, even in the presence of specific cancer antigen.⁷

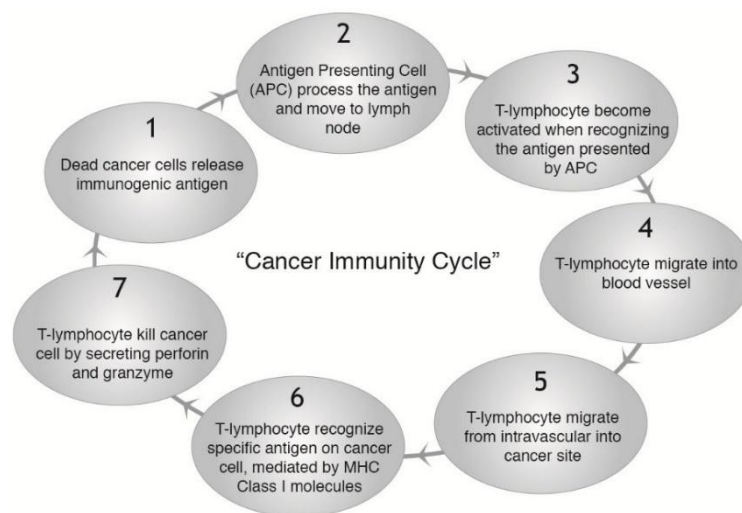


Figure 1 The Cancer Immunity Cycle. The process of cancer cells becomes immunogenic and targeted by the immune system. ²

Realizing the importance of the immune system in cancer cell's survival and eradication, scientists have developed immunotherapy to revert immunosuppressed conditions. Immunotherapy is a treatment modality that is not directly focused on killing cancer cells like chemotherapy but to harness the host's immune system, such that the immune system will attack

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the cancer cells and then develop memory cells that can prevent relapse.⁸ There are many types of immunotherapy such as checkpoint inhibitor, Adoptive Cell Therapy (ACT), therapeutic antibodies, vaccine, and virotherapy.⁴ The discussion of this paper will focus on checkpoint inhibitors and adoptive cell therapy because many clinical trials have shown that they produce clinical efficacy.

Checkpoint Inhibitors

The immune checkpoints are a physiologic mechanism to prevent excessive lymphocyte activation. There are many proteins involved in this regulation, but two proteins that have been extensively studied are Cytotoxic T-lymphocyte Associated Protein 4 (CTLA-4) (Figure 2) and Programmed Cell Death Protein 1 (PD-1) (Figure 3). Activation of lymphocyte needs at least two signals, the first signal comes from T-cell Receptor (TCR) that binds to a specific antigen which is presented by MHC class II molecules on APC, the second signal comes from CD28 on T-lymphocyte bind to CD80 on APC.⁴ After activation, CTLA-4 within the Golgi apparatus is transported to the cell membrane and bind to CD80 with a greater affinity than CD28. Without a costimulatory signal from CD28-CD80 interaction, T-lymphocyte becomes anergy.⁹ Leach, Krummel, and Allison showed that by inhibiting CTLA-4, T-lymphocyte responses are sustained, leading to cancer cell eradication.¹⁰

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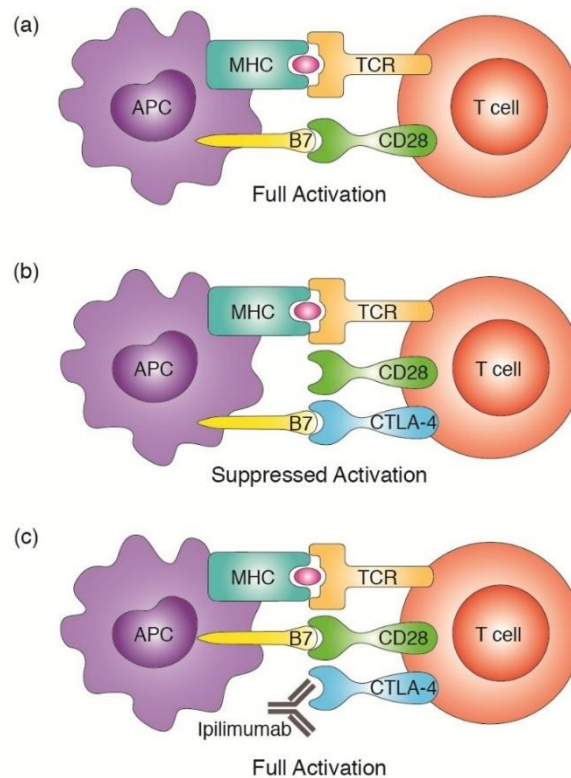


Figure 2 The CTLA-4 immune checkpoint. (a) Co-stimulatory signal by B7. (b) Inhibition by CTLA-4. (c) Checkpoint blockade by ipilimumab

The other checkpoint is PD-1. Cancer cells will increase the production of PD-1 ligand under the influence of interferon-gamma. This ligand will bind to PD-1 on the membrane of T-lymphocyte and induce T-lymphocyte inactivation and apoptosis.¹¹ Blocking of PD-1 and PD-1 ligand interaction with anti-PD-1 antibody will enhance CD4⁺ and CD8⁺ T-lymphocyte activation and proliferation.¹²

Clinical Trials of anti-CTLA-4 antibody (ipilimumab) in melanoma patients produced promising results. Hodi et al. showed that ipilimumab monotherapy gave a better median overall survival than GP-100 vaccine in unresectable stage 3-4 melanoma (10.1 vs. 6.4 months; $p = 0,003$).¹³ In this study, 10-15% of patients treated with ipilimumab suffered grade 3 or 4 side effects such as diarrhea, rash, and colitis but the severity can be reduced by corticosteroid or anti-TNF- α therapy. Robert et al. showed that, in metastatic melanoma patients, the combination of ipilimumab and dacarbazine gave higher 3-years survival rates than the combination of dacarbazine and placebo (20,8% vs. 12.2%; $p < 0,001$).¹⁴ Through an evaluation of data from 1861 metastatic melanoma patients who were treated with ipilimumab, Schadendorf et al. concluded that 22% of the patient could survive at least 3 years. This durable response gives new hope to

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advanced melanoma patients because historically, the 2-year survival rate in this group is around 10-20%.^{15,16,17}

On the other hand, ipilimumab did not give better overall survival compared to placebo in metastatic castration-resistant prostate cancer patients (11.2 vs. 10 months; $p > 0,05$).¹⁸ Other trials showed that ipilimumab did not produce any objective response in late-stage pancreatic adenocarcinoma.¹⁹ In some tumors, the main cause of immunosuppression is not CTLA-4. Further study is needed to know what type of patient characteristic that may get benefit from anti-CTLA-4.

Anti-PD-1 antibody (Nivolumab and Pembrolizumab) show promising result in various cancers. In advanced melanoma patients that were treated with pembrolizumab, the 2-year survival rate was 49%.²⁰ In advanced non-small-cell lung carcinoma (NSCLC) patients with PD-L1-positive (at least 50 % of tumor cells), pembrolizumab showed better median overall survival than docetaxel (14.9 vs. 8.2 months; $p = 0.0002$).²¹ In advanced renal-cell carcinoma patients, nivolumab showed better median overall survival than everolimus (25 vs. 19.6 months), with lesser grade 3 or 4 adverse effects in the nivolumab group (19% vs. 37%).²²

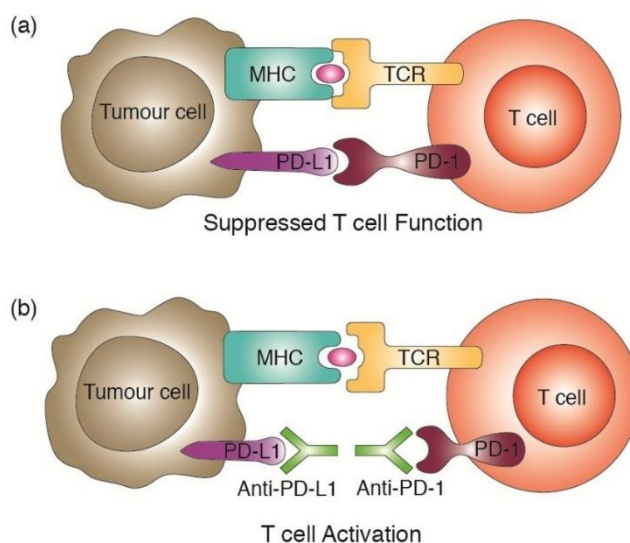


Figure 3 The PD-1 immune checkpoint. (a) Inhibition by PD-L1. (b) Checkpoint blockade by anti-PD-1 or anti-PD-L1 antibody

The treatment combination of anti-PD-1 and anti-CTLA-4 can be considered because they have different modes of action. CTLA-4 disrupts co-stimulation from APC in the early activation of T-lymphocyte in lymph nodes.²³ On the other hand, PD-1 has a role in effector phases to prevent cells from being killed by cytotoxic T-lymphocyte.²⁴ Trial combining nivolumab and ipilimumab showed a positive result in melanoma patients. The median

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progression-free survival in combination group is significantly better than the ipilimumab monotherapy group (11.5 vs. 2.9 months; Hazard ratio for disease progression = 0.42, $p < 0.001$).²⁵ However, a high percentage of grade 3 and 4 adverse effects in the combination group (55% vs. 27.3%) should be considered in choosing a treatment regimen.

Looking at checkpoint inhibitors trials that show positive clinical response and durability, there is a high chance that checkpoint inhibitors become a standard treatment, especially in advanced-stage cancer. Also, the clinical efficacy of PD-1 inhibitor in non-small-cell lung carcinoma which was considered non-immunogenic cancer may become a trigger for scientists to target other non-immunogenic tumors such as breast and colon cancer.²⁴ Furthermore, exploring other checkpoint pathways and find the best inhibitor combinations to treat certain patient characteristics will help to improve the success rate.²⁶

Adoptive T cell therapy

Adoptive cell therapy (ACT) is a method to train host T-lymphocytes in vitro to recognize a specific antigen in cancer cells, amplifying it, and then re-infuse it back to the host.²⁷ Principally, there are two methods to do it. The first method involves taking T-lymphocytes from a tumor biopsy, then culturing them with pro-proliferation cytokines such as interleukin-2.²⁸ The cultured cells are then assayed to ensure that they can recognize cancer cells. Following amplification to at least 10¹⁰ cells, T-lymphocytes are then infused back to the patients. An advantage of this method is the tumor-infiltrating lymphocyte (TIL) has been primed in vivo to recognize specific antigen on cancer cells.²⁹ However, there are some disadvantages such as lack of TIL in biopsy specimens or extracted TIL does not have a good affinity and the potential to kill cancer cells.³⁰

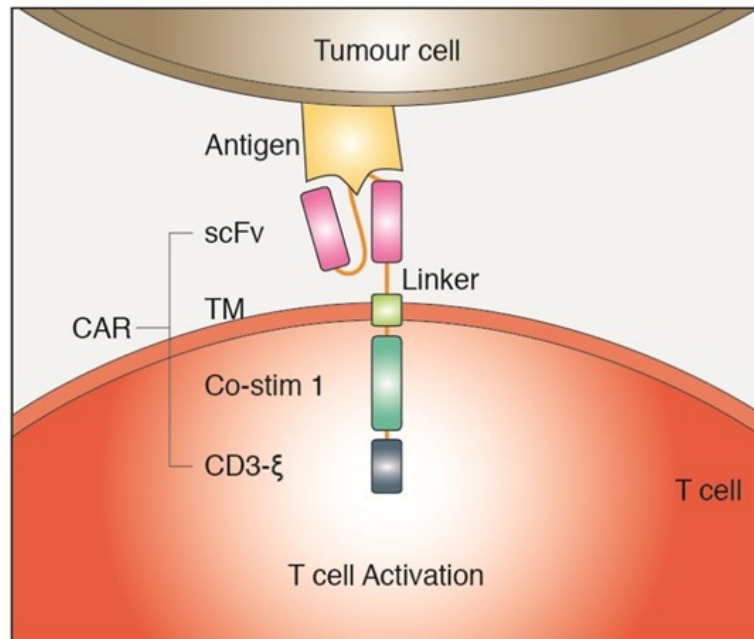


Figure 4. Chimeric Antigen Receptor (2nd Generation).

CAR can recognize antigen on the cell surface without a presentation by MHC molecules. CAR = Chimeric Antigen Receptor; scFv= Single-chain Variable Fragment; TM= Transmembrane Domain; Co-Stim 1= Co-stimulatory Domain 1.

The second method is to extract T-lymphocytes from a patient's blood and genetically modify it in vitro to express a specific receptor that can recognize specific antigen on cancer cells.³⁰ The type of receptors can be a physiologic T-Cell Receptor (TCR) which depends on the presentation of antigen by MHC class I or II molecules. The other type is Chimeric Antigen Receptors (CAR), an artificial receptor consisting of a hybrid of single-chain antibody and a signaling domain of TCR (Figure 4).³¹ Chimeric Antigen Receptor can recognize surface antigens on cell membranes without a presentation by MHC molecules.⁴ Therefore, it is very useful to attack cancer cells that downregulate the expression of MHC class 1 molecule.

The genetic engineering method makes the T-lymphocyte become a living drug that seeks and kills cancer cells without targeting essential tissue. This kind of specificity is not seen in other therapeutic modalities. The key is to find antigen that is only expressed by cancer cells, or at least the antigen is only expressed on cells that are not essential for host survival.³² Furthermore, to increase the efficacy of ACT, lymphodepletion can be done before re-infusion.³³ Lymphodepletion with chemotherapy or radiotherapy can reduce the immune suppressive effect by T-regulatory lymphocyte in the tumor microenvironment.³⁴

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On trials involving metastatic melanoma patients, tumor-infiltrating lymphocyte infusion can promote complete tumor regression in 20 of 93 (22%) patients.²⁸ Furthermore, the durable response was seen in 19 patients who remained disease-free beyond 3 years after treatment. Another milestone trial was done by Grupp et al. using second-generation CAR T (Chimeric Antigen Receptor T-lymphocyte) cells in relapsed and refractory pre-B-cell Acute Lymphoid Leukemia (ALL).³⁵ These CAR T cells recognize CD 19 which is expressed on B cells at various stages of differentiation. Both patients in this trial had complete remission; one patient still had complete remission at 11 months from treatment. Even though cytokine-release syndrome is observed in both patients, it can be managed by anti-Tumor Necrosis Factor (etanercept) and anti-Interleukin 6 (tocilizumab). Maude et al. also showed a surprising result that CAR T cells can induce complete remission in 27 of 30 (90%) leukemia patients including refractory and relapsed cases.³⁶ One of the recent trials showed that CAR T cells targeting interleukin-13 receptor alpha 2 could induce glioblastoma regression with the clinical response that persists at 7.5 months follow-up.³⁷

Analyzing all these trials, ACT can become an option, especially in relapsed or resistant cases when the current treatment options are very limited and have poor clinical efficacy. Furthermore, ACT is one form of personalized cancer therapy where “the drug” is adapted according to individual tumor characteristics. Principally, by identifying what antigen are suitable to be targeted, ACT can be implemented to treat various types of cancer.²⁷ At the moment, the best result is shown in hematologic malignancy and metastatic melanoma patients.

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Table 1 Ongoing Clinical Trials on Combination Therapy.

No.	Condition	Intervention	Phase
1	Newly-diagnosed Patients With Glioblastoma	Radiotherapy plus Nivolumab or Temozolomide	III
2	Multiple Myeloma	Nivolumab plus Pomalidomide plus Dexamethasone plus/minus Elotuzumab	III
3	Recurrent Glioblastoma or Gliosarcoma	Pembrolizumab plus Conditionally Replicative Adenovirus (DNX-2401)	II
4	Microsatellite Stable Metastatic Colorectal Cancer	Durvalumab plus Tremelimumab plus Radiotherapy	II
5	Metastatic Pancreatic Cancer	Nivolumab plus Ipilimumab plus Radiotherapy	II
6	Non-Small Cell Lung Cancer	Nivolumab plus Decitabine plus Tetrahydrouridine	II
7	Gastric Cancer	Pembrolizumab plus Chemotherapy plus Surgery	II
8	Advanced Non-Small Cell Lung Cancer	Vigil™ plus Nivolumab	II
9	Refractory Diffuse Large B-Cell Lymphoma	CD19-targeted CAR-T plus Atezolizumab	I/II
10	B-cell Hematologic Malignancy	CD19-targeted CAR-T plus CD22-targeted CAR-T	I/II

Nivolumab = anti-PD-1 antibody; Temozolomide = alkylating agent; Pomalidomide = anti-angiogenic and immunomodulator; Pembrolizumab = anti-PD-1-antibody; Durvalumab = anti-PD-L1-antibody; Tremelimumab = anti-CTLA-4 antibody; Ipilimumab = anti-CTLA-4 antibody; Decitabine = DNA methyltransferase inhibitor; Vigil™ = Augmented autologous tumour vaccine; Atezolizumab = anti-PD-L1 antibody (Source: <https://clinicaltrials.gov/> Accessed August 2018)

One obstacle to treating the solid tumor with ACT is choosing the right antigen. Targeting inappropriate antigens can promote on-target but off-tissue cytotoxicity. An example of this is a metastatic colon cancer patient who died because of respiratory distress after receiving ERBB2-specific CAR T-Cells.³⁸ Post-mortem examination of the patients showed that ERBB2 molecules are not only expressed on cancer cells but also lung epithelium. In addition to antigen selection, to kill the cancer cell, T-lymphocyte needs to infiltrate into the cancer site and to sustain its anti-tumor activity in the immunosuppressive environment.³⁹ These challenges need to be addressed in the future, probably by combination therapy.

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Immunotherapy Prospects

As stated by Chen and Mellman, cancer cells can modify its characteristic and microenvironment to build several lines of defense and nullify the immune response.² Combination therapy has been tried to overcome the different type of defense simultaneously. A combination of ACT and dendritic cell vaccination generated tumor regression in 9 of 13 (63%) metastatic melanoma patients and also enhance in vivo T-lymphocyte expansion.²⁹ The addition of immunotherapy (ACT and autologous dendritic cells) to chemotherapy as an adjuvant after primary NSCLC resection, produced a better 5-year overall survival rate than adjuvant chemotherapy alone (81% vs. 48,3%; Hazard ratio = 0.229, p= 0.0013).⁴⁰ There is a great chance that a combination of immunotherapy or a combination of immunotherapy with conventional modalities such as chemotherapy and radiotherapy can become the answer to dealing with failures in inpatient treatment. The answer will become clearer by looking at the result of the ongoing clinical trial (Table 1).

The high cost is also a major concern in immunotherapy, especially in the ACT. At the moment, many patients get to benefit from ACT by joining the clinical trials. If the trial succeeds and the treatment becomes commercialized, there will be cost issues associated with the treatment. At present, for CAR T therapy, it is estimated to be 250,000 USD per patient which is unaffordable for the general population.⁴¹ Therefore a better manufacturing process is needed to reduce the cost. One example proposed is by using the piggyBac transposon system instead of retroviral or lentiviral vectors for gene modification.⁴²

Conclusion

In the past, people who were diagnosed with chemoradiotherapy resistant cancer did not have many choices of treatment to prolong their lives. However, immunotherapy brings new hope that can promote durable remission with manageable side effects. Even though there are still many challenges needed to be solved, with the current evidence we can assure that immunotherapy is not merely hype. Through extensive research, there is a great chance that cancer can be managed by immunotherapy or combination therapy involving immunotherapy.

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