ความก้าวหน้าด้านภูมิคุ้มกันบำบัดมะเร็ง: การก้าวข้ามข้อจำกัดในการรักษาแบบเดิม

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บทคัดย่อ

การรักษามะเร็งทั่วไปมีหลายวิธี ได้แก่ เคมีบำบัด การฉายรังสี การผ่าตัด ซึ่งวิธีเหล่านี้มีปัญหาและข้อจำกัด ตัวอย่างเช่น การเกิดความเป็นพิษจากการรักษาด้วยเคมีบำบัด ได้แก่ สภาวะลดการผลิตเซลล์เม็ดเลือดในไขกระดูกและโรคระบบประสาท เซลล์มะเร็งดื้อต่อการรักษาด้วยเคมีบำบัดซึ่งทำให้การรักษาล้มเหลว และการรักษาแบบไม่จำเพาะต่อเซลล์มะเร็งด้วยวิธีการฉายรังสีหรือการผ่าตัดซึ่งทำลายเซลล์ปกติที่อยู่รอบๆและสามารถนำไปสู่การติดเชื้อ การรักษามะเร็งด้วยภูมิคุ้มกันบำบัดได้ถูกคิดค้นเพื่อใช้รักษาด้านเนื้องอกหรือมะเร็ง เป็นวิธีที่จำเพาะและมีผลข้างเคียงน้อยซึ่งมีเป้าหมายต่อเซลล์มะเร็งโดยตรงและมีหลายวิธี เช่น ตัวยับยั้งการทำงานที่อิมมูนเช็คพอยต์ซึ่งเป็นโมโนโคลนอลแอนติบอดีที่ขัดขวางการส่งสัญญาณยับยั้งการตอบสนองทางภูมิคุ้มกันจากเซลล์มะเร็ง การรักษาด้วยคาร์ที-เซลล์ โดยนำเซลล์เม็ดเลือดขาวชนิดที-เซลล์มาตัดต่อทางพันธุกรรมให้มีโมเลกุลรับสัญญานเพื่อจับแอนติเจนของเซลล์มะเร็งทำให้เซลล์มะเร็งถูกทำลาย และวัคซีนรักษามะเร็งซึ่งกระตุ้นให้ระบบภูมิคุ้มกันรู้จักแอนติเจนที่เกี่ยวกับมะเร็ง บทความฉบับนี้ได้ทำการรวบรวมความก้าวหน้างานวิจัยและความรู้ทางด้านภูมิคุ้มกันบำบัด

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Advances in Cancer Immunotherapy: Overcoming the Limitations of Conventional Treatments

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Abstract

Conventional cancer treatments, such as chemotherapy, radiation therapy, and surgery, present various limitations and challenges, for instance, toxicity of chemotherapy such as myelosuppression and neuropathy, chemotherapy-resistant cancer cells caused treatment failure, and non-specific targeting of cancer cells with radiation therapy or surgery damages to surrounding healthy tissues lead to infection. Cancer immunotherapy has emerged as a promising approach in the field of oncology, offering specific treatment options and less side effect. This approach targets cancer cells directly through various strategies, including immune checkpoint inhibitors, which are monoclonal antibodies that block inhibitory signals on immune responses from cancer, chimeric antigen receptor (CAR) T-cell therapy that T-cells were genetically engineered to express receptors for cancer antigen recognition result in the destruction of cancer cells, and cancer vaccines that stimulate the immune system to recognize cancer-associated antigens. This

review provides recent research advancements and the knowledge base on cancer immunotherapy.

Keywords: Immunotherapy/ CAR-T cell/ Adoptive Cell Therapy/ Monoclonal Antibody/ Cancer vaccine

Introduction

Cancer is a non-communicable disease that poses a significant global health challenge due to its increasing incidence and mortality rates [1]. In Thailand, the mortality rate of all types of cancer was reported as the highest rate, with rates of 123.3, 128.2, 129.5, 128.5 and 127.9 per 100,000 people from 2018 to 2022 [2]. Cancer immunotherapies have revolutionized the treatment landscape for various malignancies by enhancing the immune response to target and destroy cancer cells, offering specific treatment options and fewer side effects compared to conventional treatments. Immunotherapies present a promising strategy to improve survival rates and reduce cancer-related morbidity and mortality worldwide. This review summarizes recent research advancements and the current knowledge base on cancer immunotherapy, providing valuable insights for further research.

1. Cancer Pathogenesis

Cancer is caused by the uncontrolled proliferation of abnormal cells, which can invade and destroy surrounding tissues and spread to other parts of the body through the blood and lymph systems that affecting to organ function [3]. The disease has been classified into 4 stages [4], including

Stage 0: Carcinoma In Situ

Cancer staging begins with Stage 0, also known as carcinoma in situ. At this preliminary stage, abnormal cells are detected but remain confined to the layer of cells where they originated. These cells have not invaded neighboring tissues or metastasized to other parts of the body. Early detection at Stage 0 is important because it often allows for interventions that can effectively remove or control the abnormal cells, thereby preventing progression to more invasive stages. This stage is not classified as cancer but is considered a pre-cancerous condition.

Stage I: Localized Cancer

Cancer is characterized by a localized tumor that has not penetrated into adjacent tissues and has not spread to lymph nodes or distant sites. The tumor is typically small and confined to its original location. The prognosis at this stage is favorable, with a high potential for successful treatment outcomes. Therapeutic approaches at Stage I often involve surgical resection of the tumor. (Figure 1)

Stage II and III: Regional Spread

Stages II and III represent more advanced cancer with regional spread. These stages are differentiated by the extent of tumor growth and lymph node involvement. At Stage II, the tumor is larger than in Stage I and divides rapidly (Hyperplasia) resulting in an increase in cell numbers and may have begun to invade nearby lymph nodes, but it has not yet spread to distant body parts. At Stage III, the cells display abnormal morphology, which change in size, shape, and organization (Dysplasia), and become cancer cells. Treatment strategies become more aggressive, often combining surgery with other therapies such as radiation or chemotherapy.

Stage IV: Metastatic Cancer

Stage IV represents the most advanced stage, known as metastatic cancer. At this stage, cancer has spread from its original site to distant organs and tissues, such as the bones, liver, lungs, or brain. The prognosis for stage IV cancer is more cautious, and treatment goals shift from curative to palliative. The emphasis is on controlling symptoms, enhancing quality of life, and prolonging survival. Treatment options may include conventional therapies as well as promising approaches such as targeted therapy and immunotherapy.

There were many factors that caused cancer, for example genetic mutation, environment, lifestyle and infections. Genetic mutations play a crucial role in the development of cancer. These mutations can be inherited or acquired. Inherited mutations, such as deletions, insertions, fusions, or

DNA methylation [5], can significantly increase the risk of developing cancers. For example, inherited mutations in the *BRCA1/BRCA2* genes increase the risk of breast and ovarian cancer. Acquired mutations, which occur due to errors in DNA replication or exposure to carcinogens, can also contribute to cancer development. For instance, mutations in the *TP53* gene, which plays an important role in DNA mismatch repair, are commonly found in a wide range of cancers and are associated with poor prognosis [6].

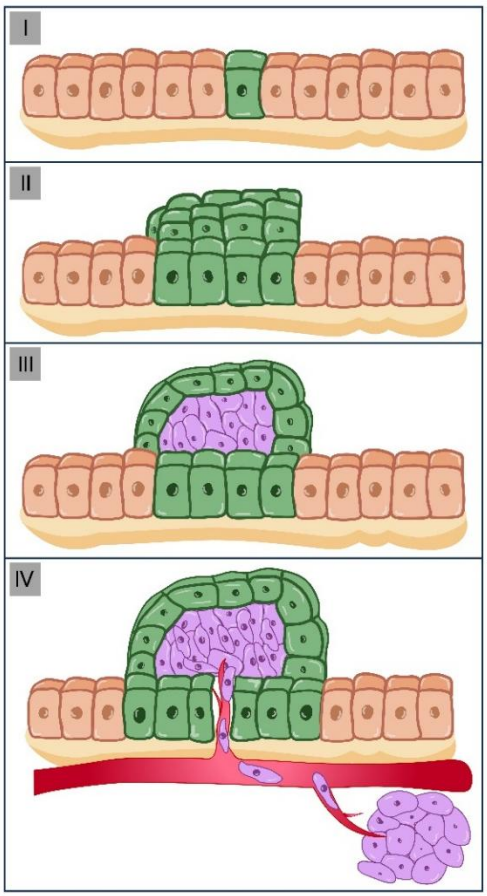

Figure 1 Stage of tumorigenesis. **I.** Genetic mutations in epithelial cell (green) and the cell has not penetrated into adjacent tissues **II.** Cell divides rapidly (Hyperplasia). **III.** Atypical hyperplasia (Dysplasia) turns into cancer cells (purple). **IV.** Cancer cells spread to other tissues and organs (Metastasis).

Environmental exposures elevate risk for cancer. Carcinogens such as tobacco smoke, ultraviolet (UV) radiation, and inorganic compounds can damage DNA and promote cancer formation. Tobacco smoke has been associated with lung cancer, contributing to approximately 18.7% of cancer deaths worldwide [7]. UV radiation is a well-known cause of skin cancers, including melanoma and squamous cell carcinoma, due to its ability to induce DNA damage in skin cells. Additionally, exposure to chemical carcinogens, such as asbestos and benzene, has been shown to cause cancers such as mesothelioma and leukemia, respectively [8].

Lifestyle is one of the factors that can influence cancer development. Diets high in red and processed meats have been associated with an increased risk of colorectal cancer because of the presence of carcinogenic compounds formed during meat processing [9]. Conversely, diets rich in fruits, vegetables, and whole grains have protective effects against various cancers. Physical inactivity is another risk factor, with studies showing that regular exercise can reduce the risk of cancers such as breast and colon cancer by regulating hormone levels and improving immune function [10]. Excessive alcohol consumption was involved to cancers of the mouth, throat, esophagus, liver, and breast, potentially due to its ability to cause direct cellular damage, alter in folate metabolism, and interfere with DNA repair [11].

Several viruses, bacteria, and parasites can induce cancer through several mechanisms, including chronic inflammation, immune suppression, direct cellular transformation, and the insertion of oncogenic viral genes into host genomes. Human papillomavirus (HPV) is implicated in nearly all cases of cervical cancer and a significant proportion of other anogenital and oropharyngeal cancers. Hepatitis B and C viruses are major risk factors for liver cancer, with chronic infection leading to cirrhosis and subsequent

malignant transformation of liver cells. The bacterium *Helicobacter pylori* is associated with stomach cancer due to its role in causing chronic inflammation and ulcers in the gastric lining [12].

2. Conventional cancer treatments

Conventional cancer treatments, including surgery, chemotherapy, and radiation therapy, are standard approaches that have provided substantial benefits in cancer management. However, these treatments have limitations and challenges.

Surgical resection is often the first-line treatment for solid tumors. While it may not be feasible for metastatic cancers and postoperative complications, such as infections and bleeding, are common and can significantly affect patient outcomes.

Chemotherapy employs cytotoxic drugs to kill rapidly dividing cancer cells, but its efficacy is often limited by systemic toxicity. The clinical feature of toxicities is wide, ranging from mild toxicities, such as nausea, vomiting, dysgeusia, and hair loss, to severe effects, such as myelosuppression, gastrointestinal disturbances, and neuropathy, that can severely affect patients' life and lead to fatal outcomes [13]. Cancer cells can become resistant through various mechanisms, including expression of drug pumps, increased ability to repair DNA damage, reduced susceptibility to apoptosis and altered expression of drug-metabolising enzymes, making chemotherapy was less effective [14]. Another significant limitation is the non-specific nature of chemotherapy, which damages healthy host cells, especially immune cells, leading to widespread side effects.

Radiation therapy uses high-energy particles to destroy DNA in cancer cells. One significant issue is the damage to surrounding healthy tissues, which can lead to acute and chronic side effects, such as pneumonitis, dermatitis, calcified

lymph nodes, fibrosis, atrophy, necrosis, and vascular damage. Radiation can induce severe complications like secondary malignancies [15].

3. Cancer Immunotherapy

Cancer immunotherapy has been developed to treat cancer by improving the immune system's natural ability to eliminate cancer cells. Several clinical studies have evaluated the immunotherapy approaches, including adoptive cell therapy, monoclonal antibody therapy, chimeric antigen receptor (CAR)-T cell, small molecule drug Immunotherapy and cancer vaccines, which provide high potential and specificity and less side effect.

Adoptive Cell Therapy

Adoptive Cell Therapy is an approach that employs lymphocytes collected from resected tumor specimen, called tumor-infiltrating lymphocytes. Tumor-infiltrating lymphocytes were isolated and expanded *ex vivo* in growth medium with IL-2, anti-CD3, OKT-3 monoclonal antibody, phytohemagglutinin. Then, tumor-infiltrating lymphocytes cultures were re-infused into the patient (Figure 2). The whole manufacturing process takes 6–8 weeks. Studies showed adoptive T-cell therapy is an effective treatment for metastatic melanoma [16].

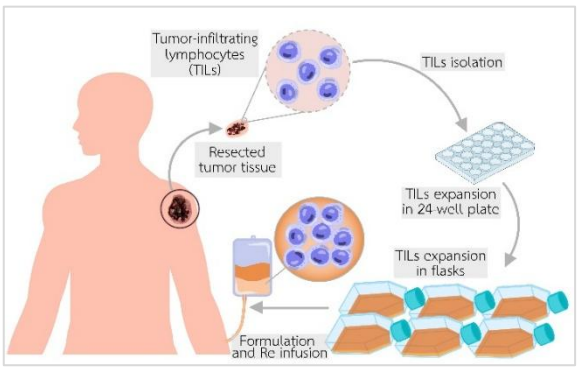

Figure 2 Manufacturing process of Adoptive Cell Therapy. Tumor-infiltrating lymphocytes (TILs) are isolated from resected tumor sample, then expanded *ex vivo*, followed by TILs formulation and re-infusion into patient.

Chimeric antigen receptor (CAR)-T cell therapy

Chimeric antigen receptor (CAR)-T cell therapy has emerged as an approach to cancer treatment using T cells that are genetically engineered to express chimeric antigen receptors (CARs), which specifically recognize and bind directly to antigens on the surface of cancer cells to eliminate them without antigen processing and presentation through MHC molecules. CARs are synthetic receptors composed of the following components: 1. An extracellular antigen-recognition domain, which is a single-chain variable fragment (ScFv). 2. A hinge domain, which is located between an extracellular domain and a transmembrane domain and plays a role in signaling threshold regulation 3. A transmembrane domain 4. An intracellular domain. After antigen binding, the CARs generate signals that result in activation of T cells, initiating an immune response [17].

The engineering of CARs has evolved to include multiple generations, each with enhanced features to improve T cell activation. The first-generation CARs consisted of a single signaling domain, CD3ζ, which is the core component that contains three immunoreceptor tyrosine-based activation motifs (ITAMs) (Figure 3). The first-generation provided initial function but showed low performance in cytotoxicity, proliferation and cytokine signaling. Second-generation CARs incorporated a co-stimulatory domain, such as CD28 or CD137 (4-1BB), which significantly enhanced T cell proliferation and cytotoxicity. The third-generation CARs were developed from the second generation by adding two co-stimulatory domains such as CD28 with CD137 (4-1BB) or CD134, further increasing T cell activity and persistence [18]. The fourth-generation CARs further expanded on the second generation by adding a cytokine inducer to activate cytokine secretion, such as IL-12, which promoted tumor eradication though several synergistic mechanisms such as cytotoxic granule exocytosis (perforin and

granzymes) or death ligand–death receptor (Fas–FasL). The fifth-generation CARs were based on the second generation, but incorporated an additional signaling domain, a truncated cytoplasmic IL-2 receptor β-chain domain with a binding site for the transcription factor STAT3, thus this CARs simultaneously triggered three synergistic signals, including a signaling domain (CD3ζ), co-stimulatory domain (CD28) and cytokine (JAK–STAT3/5), required to promote T cell activation and proliferation [19].

CAR-T cell therapy showed remarkable success in treating B-cell malignancies, including B cell non-Hodgkin's lymphoma, Hodgkin's lymphoma and B cell acute lymphoblastic leukemia, that CAR-T cell was designed to recognize CD19, CD20 or CD30 antigens on tumor cell [20]. The human epidermal growth factor receptor 2 (HER2) was reported to be over-expressed in metastatic colorectal cancer and provided evidence for a promising target in CAR-T cell [21]. Despite these successes, the application of CAR-T cell therapy to solid tumors has been more challenging, primarily due to the immunosuppressive tumor microenvironment and heterogeneity of antigen expression.

Toxicities caused by CAR-T cells have been reported. One significant issue was cytokine release syndrome (CRS) triggered by infused CAR-T cells cause a systemic inflammatory response that can lead to organ damage. Additionally, neurotoxicity has been observed in some patients. The design of CARs for binding type of antigen is also important since CAR-T cells can potentially damage normal cells by targeting tumor-associated antigens (TAA) that are also expressed on those cells. Therefore, CARs targeting tumor-specific antigens (TSA), which are expressed on cancer cells but not on normal cells, can increase specificity and efficiency of the treatment [22].

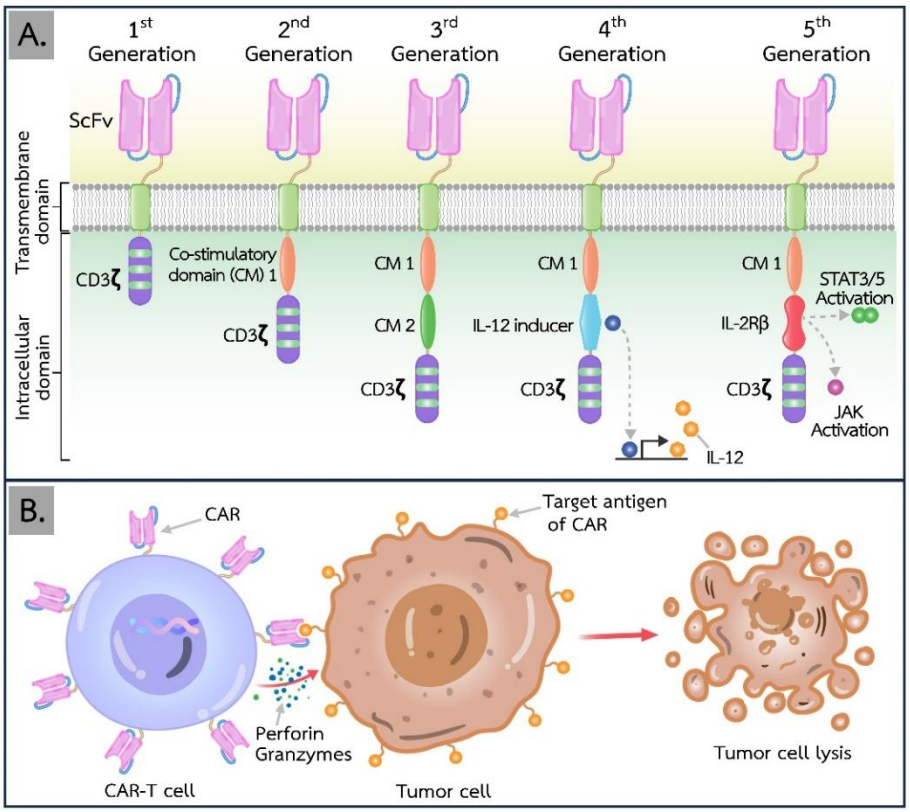

Figure 3 A.) Structure of CAR generation. The first-generation CARs contained a signaling domain (CD3ζ) in the intracellular domain. The second-generation CARs included one CM 1, such as CD28, 4–1BB and CD134, whereas the third-generation CARs contained CM 1 and CM 2. The fourth-generation of CARs was based on second-generation CARs paired with a cytokine inducer to secrete cytokine (e.g. IL-12). The fifth-generation CARs, is also based on the second generation of CARs, but incorporate a truncated cytoplasmic IL-2 receptor β-chain domain that activated signaling pathways (e.g. JAK and STAT3/5). **B.)** CAR-T cells released perforin and granzymes led to tumor cell lysis. ScFv; single-chain variable fragment, CAR; Chimeric antigen receptor, CM; co-stimulatory domain.

Monoclonal Antibody Therapy

Monoclonal antibody therapy is a therapeutic approach that employs the specificity of antibodies to target molecules involved in disease processes. Monoclonal antibodies are designed to recognize and bind to antigens present on the surface of cancer cells, allowing them to activate immune cells, such as NK cell, Macrophage, Dendritic cell, Gamma Delta T Cell and Cytotoxic T cell, to eliminate cancer cells, or inhibit cellular signaling pathways crucial for cancer growth. For instance, Trastuzumab has revolutionized the management of HER2-positive breast cancer, significantly improving patient outcomes. Rituximab, which is a chimeric monoclonal antibody recognized the CD20 molecule on the surface of B cells, showed efficacy in B cell lymphoma, rheumatoid arthritis and systemic lupus erythematosus [23].

Additionally, Monoclonal antibodies, called immune checkpoint inhibitors, were designed to block receptors that sent inhibitory signals caused immunosuppressive mechanisms exploited by tumors. Blocking these receptors allows cytotoxic T cells to kill cancer cells. The US FDA has approved immune checkpoint inhibitors such as PDL-1 inhibitors (Atezolimumab, Durvalumab and Avelumab), PD-1 inhibitors (Nivolumab, Pembrolizumab, and Cemiplimab), and CTLA-4 inhibitor (Ipilimumab). Several studies had reported success in treating patients with metastatic melanoma, non-small lung cancer, head and neck cancers and renal cell carcinoma [24]. This therapy improves significant promise in enhancing the precision of cancer treatment, as it selectively targets malignant cells, and demonstrated remarkable efficacy in various cancer types, often in combination with conventional treatments [24].

Cancer Vaccines

Preventive cancer vaccines have been showed effective to prevent viral infection with high carcinogenic relevance, such as human papillomavirus (HPV) vaccine that has significantly reduced the incidence of cervical cancer [25].

Sipuleucel-T, a type of therapeutic cancer vaccine approved by the U.S. FDA, has showed improved survival outcomes of prostate cancer. The method isolates antigen-presenting cells (APCs), such as dendritic cell, from a patient's blood. These cells were expanded and activated *ex vivo* with a prostate antigen, which is a prostatic acid phosphatase fused to granulocyte–macrophage colony-stimulating factor, and then re-infused into the patient. This procedure aims to enhance the capabilities of APCs to stimulate cytotoxic T-cell response against cancer cells [26].

Viral vector-based vaccines leverage modified viruses to deliver cancer antigens to the immune system. Talimogene laherparepvec (T-VEC), an oncolytic herpes simplex virus type 1 (HSV-1) modified to express granulocyte-macrophage colony-stimulating factor (GM-CSF), was approved by the U.S. FDA for the local treatment of melanoma. T-VEC Mechanism of action is replication within tumor cells causing tumor cell lysis. The role of GM-CSF is to enhance systemic anti-tumor immunity [27].

Conclusion

Cancer immunotherapies have revolutionized the treatment landscape for various malignancies by enhancing the immune response against tumors and have shown promising clinical efficacy. Their ability to target cancer cells specifically while minimizing damage to normal cells has improved patient outcomes. However, several challenges remain, including the management of immune-related adverse events and cost.

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