The Gulf Journal of Oncology is published with the financial support from the Kuwait Foundation for the Advancement of Sciences.

Indexed By PubMed and Medline Database

The Official Journal of the Gulf Federation For Cancer Control
## Table of Contents

### Original Articles

**Spectrum of Breast Diseases: Histopathological and Immunohistochemical Study from North India**
Sumyra Khurshid Qadri, Pranjali Sejwal, Rashmi Priyadarshni, Milan Jaiswal, Ruchi Khandewal, Manisha Khanna, Tanu Agarwal, Hema Pant, Ratana Saxena

**Concurrent Paclitaxel and Radiotherapy for Node Positive Breast Cancer**
Asmaa Ali Hassan, Noha Yehia Ibrahim, Mohamed Abdel Rahman Kassem, Abdel Aziz Mostafa Toeama

**Cancer Control Priorities and Challenges in Saudi Arabia: A Preliminary Projection of Cancer Burden**
Maha T. Alattas

**A Novel Approach to Obtain Follow-up Data on the Vital Status of Registered Cancer Patients: The Kuwait Cancer Registry Experience**
Eiman Alawadhi, Ahmed Al-Awadi, Amani Elbasmi, Michel P. Coleman, Claudia Allemani

**Cancer survival trends in Kuwait, 2000–2013: A population–based study**
Eiman Alawadhi, Ahmed Al-Awadi, Amani Elbasmi, Michel P. Coleman, Claudia Allemani

**Triple Negative Breast Cancer: 10-Year Survival Update of The Applied Treatment Strategy in Kuwait**
Salah Fayaz, Gerges A. Demian, Mustafa El–Sherify, Heba Eissa, Mary Aziz, Sadeq AbuZallouf

**Early Calcium Supplementation After Total Thyroidectomy Can Prevent Symptomatic Hypocalcemia**
– Findings from a Retrospective Study
Manu Santhosh, Sajith Babu Thavarool, Sandeep Vijay, Adharsh Anand, Guru Charan Sahu, v Satheeshan Balasubramaniam

**Association between nodal metastasis and histopathological factors in postoperative gingivo–buccal complex squamous cell carcinoma: A Retrospective Study**
Sweta Soni, Tej Prakash Soni, Nidhi Patni

### Review Articles

**Impact of HPV on the Pathobiology of Cancers**
Ritesh Kumar, Pranay Tanwar, Angel Rajan Singh, Showket Hussain, G.K. Rath

**Cancer Immunotherapy: An Updated Overview of Current Strategies and Therapeutic Agents**
Osama Abu–Shawer, Tariq Bushnaq, Mohammad Abu–Shawer

### Case Reports

**Extremely Giant Ovarian Mucinous Cystadenoma**
Abdulaziz Alobaid, Heba Elamir, Mohammed Abuzaid, Ahmed Abu–Zaid

**Hemorrhagic Brain Metastasis as the Initial Manifestation of Esophageal Adenocarcinoma**
Hussein Algahtani, Bader Shirah, Yehya Seddeq, Hatim Al–Maghraby

### Conference Highlights/Scientific Contributions

- **News Notes**
- **Advertisements**
- **Scientific events in the GCC and the Arab World for 2019**
Cancer Immunotherapy: 
An Updated Overview of Current Strategies and Therapeutic Agents

Osama Abu–Shawer¹, Tariq Bushnaq¹, Mohammad Abu–Shawer²

¹ School of Medicine University of Jordan, Amman, Jordan
² Clinical Research Office King Hussein Cancer Center, Amman, Jordan

Abstract

After several years of discouraging results, immunotherapy finally becomes a powerful, clinically valid and approved treatment for numerous types of cancer. Immunotherapy involves treatment approaches that work in various ways; some boost the body’s immune system while others help guide and direct the immune cells to attack cancer cells specifically. In this review article, we summarize the current cancer immunotherapy strategies; immune checkpoint blockade, adoptive cellular therapy, cancer vaccines, oncolytic viruses, and the monoclonal antibodies and discuss the recent progress and future trends of the combination therapies.

Keywords: Immunotherapy, T–Cell, PD–L1, CTLA–4 and CAR–T.

Introduction

Exploiting the immune system to fight cancer is an old idea that emerged several decades ago and depends on the fact that the immune cells can identify and kill the malignant cells via a process called immune surveillance (¹). Malignant tumors grow through a process of carcinogenesis which consists of several genetic changes that lead to immortality; but these changes also generate many foreign antigens which are responsible for making the malignant cells detectable by the host’s immune system. Despite the fact that the host’s immune system can detect the differences in the surface antigens, malignant cells keep coping to escape the recognition by the immune surveillance and consequent destruction. (²) To accomplish this, cancer cells develop several resistance strategies, including the evasion of local immune response, deactivation of T cell signaling pathways, and induction of immune tolerance. Furthermore, the immunoediting process, the emergence of less immunogenic antigens due to frequent immune recognition and response to the tumor antigens, can also help cancer cells to escape the immune surveillance (³).

It is a well–known fact for several decades ago that malignant cells can suppress the anti–tumor immune response by several mechanisms, and that is why the classic cancer treatments rely on other tools, such as chemotherapy, radiotherapy and surgery. Currently, it is well–established that different components of the immune system could play essential roles in fighting against cancer. (⁴) After long history of numerous discouraging attempts and clinical failures, the cancer immunotherapy field has received significant amount of boosts, started primarily by the FDA approval of ipilimumab (Anti–CTLA–4) for melanoma treatment (⁵) and will not end on the approval of Chimeric Antigen Receptor T–Cell Therapy (CART) for acute lymphoblastic leukemia ALL and refractory large B–cell lymphoma more recently (Table–1). These successes have shed the light on the limitless roles the immunotherapy can play in cancer treatment.

Cancer immunotherapy includes different approaches, ranging from suppressive to stimulating mechanisms. Activating mechanisms of the immune system include tumor antigens vaccination to expand the tumor antigens presentation which will launch an effective response against cancer cells, adoptive cellular therapy which indicates administration of immune cells directly to the patients, the administration of oncolytic viruses for initiating a systemic anti–tumor immune response, and the administration of special cytokines to boost T–cell activity against cancer cells. Suppressive mechanisms include immune–checkpoint inhibitors such as anti–PD1,
anti–PD–L1 and anti–CTLA–4, in addition to the monoclonal antibodies that target CD25–T cells \(^{(6)}\)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune Checkpoint Inhibitors:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD–1 inhibitors</td>
<td>Melanoma, NSCLC, HL, Gastric, Bladder, Head &amp; Neck Cancer</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD–1 inhibitors</td>
<td>Melanoma, RCC, NSCLC, CRC, HCC, Bladder, Head &amp; Neck Cancer</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD–L1 inhibitors</td>
<td>Bladder, NSCLC</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD–L1 inhibitors</td>
<td>Bladder, Merkel Cell Cancer</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>PD–L1 inhibitors</td>
<td>Bladder, NSCLC</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>CTLA–4 inhibitor</td>
<td>Melanoma</td>
</tr>
</tbody>
</table>

**Adoptive Cellular Therapy:**

| CAR–T cellular therapy | Modified T Cell | ALL, NHL                                        |

**Cancer Vaccination Therapy:**

| Sipuleucel–T           | Dendritic cells–based vaccine | Prostate Cancer |

**Oncolytic Viral Therapy:**

| Talmogene laherparepvec | GM–CSF expressing virus | Melanoma |

**Monoclonal Antibodies:**

| Alemtuzumab            | Anti–CD52               | ALL     |
| Trastuzumab            | Anti–HER2               | Breast Cancer |
| Ibritumomab tiuxetan   | Radiolabelled Anti–CD20 | NHL     |
| Brentuximab vedotin    | Chemo–attached Anti–CD30 | HL      |
| Blinatumomab           | Anti–CD3 & Anti–CD19    | ALL     |

Table 1. FDA Approved Immunotherapeutics

**Immune Checkpoint Blockade**

Cancer cells have a huge number of gene mutations, which are responsible for producing a lot of new proteins known as tumor antigens. Despite the observed immune response against cancer cells in lab models, the real immune response is not so effective because cancer cells induce tolerance among the effector T cells and express ligands that inhibit T cells activity inside the tumor microenvironment \(^{(1)}\). Checkpoint blockade is an approach to stimulate the anti–tumor immune response by blocking the immune–inhibitory ligands and pathways expressed and launched by cancer cells \(^{(2)}\) (Figure–1 A & B).

Effector T cells express some co–inhibitory receptors (cytotoxic T–lymphocyte–associated Antigen–4 CTLA–4, programmed cell death protein–1 PD–1, lymphocyte–activation gene 3 LAG–3, and the latency–associated peptide LAP). The vast majority of immune checkpoints include ligand–receptor interactions; thereby developing recombinant antibodies to bind the ligands or receptors was the best way to block their interaction. The antibodies target CTLA–4, were the first FDA approved type of immunotherapy \(^{(6)}\).

CTLA–4 is solely expressed on T cells; it functions in regulating the extent of T cell activation in different stages. Also, it counteracts the CD28 which is a co–stimulatory receptor amplifies T cell receptor TCR signaling pathway to launch T cell activity immediately after the antigen recognition. \(^{(8)}\) On the other hand, CTLA–4 expression on T regulatory cells triggers and facilitates their suppressive function. Therefore, CTLA–4 blockade plays a vital role in both the enhancement of CD4 T cells activity and the impedance of T regulatory cells dependent.
Current Cancer Immunotherapeutics, Osama Abu—Shawer, et. al.

immunosuppression. (7) (Figure—2 A & B) Ipilimumab is a monoclonal antibody targets CTLA—4 approved by FDA to treat metastatic melanoma. Because ipilimumab induce non—specific activation of the immune system, it may occasionally cause serious and dangerous side effects. (9)

Programmed death protein 1 (PD1) is an inhibitory receptor expressed on activated T cells. The interactions between T cell PD1 receptor and its ligands PD—L1 or PD—L2, which expressed on many types of cancer cells, activate specific pathways that ultimately inhibit T cells activity and diminish the anti—tumor immune response. (10) Therefore, the administration of antibodies that target and block PD1, PD—L1, or PD—L2 can re—activate and stimulate T cells activity and their anti—tumor immune response. (7)

Pembrolizumab and Durvalumab are monoclonal antibodies that target PD1 and PD—L1 and help in treating many types of solid tumors, including melanoma, kidney cancer, non—small cell lung cancer NSCLC, head and neck cancers, bladder cancer and in a specific type of hematological malignancy which is the refractory classical Hodgkin lymphoma. (11)

**Combination Therapies**

Only a minor group of patients with metastatic cancers may benefit from a single immunotherapy, but for the vast majority of such patients, monotherapy will be relatively ineffective. Therefore, the combination of different therapeutic agents is required to achieve the desired remission for those patients with advanced cancer stages. The field of combining immune checkpoint inhibitors is growing rapidly to the degree that new combinations evaluated almost every month. (5) Despite the fact that both PD1 and CTLA—4 expressed on T cells, these inhibitor molecules affect various signaling pathways inside T cells. Thus, anti—CTLA—4 and anti—PD1 combination therapy have been expected to show a strong synergy. (12) Actually, the combination therapy was tested clinically and showed a significant improvement of the anti—tumor responses. (13)

The adverse effects of chemotherapy protocols have been considered for a long time as certainly harmful to the immune system in general and the anti—tumor immune response in particular. (1) Actually, conventional cytotoxic chemotherapy regimens may potentiate systemic anti—tumor immune response by releasing many tumor antigens into the circulatory and lymphatic systems. (14) Also, chemotherapy administration may boost the efficacy of immunotherapies by amending the tumor immunosuppressive environment. Cyclophosphamide is known for depleting T regulatory cells, while other chemotherapeutic drugs, such as 5—fluorouracil and paclitaxel, may eliminate myeloid—derived suppressor cells MDSCs. Therefore, chemotherapy may enhance the anti—tumor capacity of T cells and contribute in initiating effective anti—tumor immune responses by discouraging the immunosuppressive functions of T regulatory cells and MDSCs. Additionally, combining immune checkpoint inhibitors with chemotherapy may take advantage of the reduction of tumor burden caused by chemotherapy. (12) However, some chemotherapeutic agents suppress cytotoxic T cells responses which result in a negative impact on the efficacy of immune checkpoint blockers that promote the activation and proliferation of these cells. Thus, a great caution should be taken when...
such chemotherapeutic agents combined with immune checkpoint inhibitors. (1)

**Adoptive Cell Therapy**

T cellular therapy is barely a new concept. In fact, we have been practicing T cell therapy for over 5 decades as an essential part of allogeneic hematopoietic stem cells transplantation, where the passive transfereff of T cells used for rebuilding the ablative hematopoietic stem cells system and mediating cytotoxic effects against leukemic cells which is the cornerstone of the success of this approach. (18) Adoptive cellular therapy is a novel type of immunotherapy which invests the anti-tumor capacity of T cells to terminate and kill cancer cells. Adoptive cell therapy has demonstrated its capability of inducing dramatic responses over the last decades and has been an encouraging therapeutic option. (19) Recently, using gene therapy tools has improved the efficacy of this approach by creating modified T cells that can identify and attack cancer cells selectively. Currently, there are two well-established approaches for directing modified T cells against cancer cells. (20)

The first approach depends on T cells isolated from the local tumor environment known as tumor infiltrating lymphocytes (TILs). After extensive ex-vivo expansion of the tumor infiltrating lymphocytes, the expanded T cells then re-infused collectively into the patient. TIL approach has shown a remarkable anti-tumor response, particularly in advanced melanoma, where around one-third of patients showed durable remissions lasting several years. (21)

The second approach of adoptive T cell therapy depends on the ability to modify T cells genetically to become able to identify and terminate cancer cells. In this approach, circulating T cells collected from the patient’s blood engineered to produce special receptors called chimeric antigen receptor CAR which consists of an Immunoglobulin variable domain fused to the constant domain of T cell receptor TCR, expanded in the lab, and then re-infused back into the patient’s circulation. (22) CAR – T cells will identify and attach to specific cancer cell surface antigen called CD19. Thereby, chimeric antigen receptor directs and boosts the cytotoxic capacity of modified T cells against CD19+ cancer cells. Currently, there are two types of cancer that can be managed by CAR – T cellular therapy: acute lymphoblastic leukemia ALL and refractory large B-cell lymphoma. (23)

**Cancer Vaccines**

Historically, the first approach to activate T cells to fight against the tumor cells was the cancer antigens vaccination. The fact that patients harbor T cells capable of identifying tumor antigens and the successful use of vaccines in the defense against the carcinogenic infectious diseases, such as hepatitis B virus HBV and human papillomavirus HPV have opened the door in front of developing effective cancer vaccines. (1) However, cancer’s ability to suppress the immune response by inducing tolerance to the tumor antigens limits the effectiveness of any cancer vaccine. Therefore, cancer vaccines have to break the induced tolerance in order to be effective. (24)

The main obstacles in developing successful cancer vaccines are the inability of identifying the most immunogenic antigens to use and the inability of activating the antigens presenting cells to load and present the vaccine antigens. (25) Thus, without a proper activating adjuvant, antigens presenting cells would remain in their steady state and would probably develop tolerance. (24) Actually, all classic cancer vaccine formulations, which contained only short peptides of tumor antigens without activating adjuvant for antigens presenting cells, were clinically ineffective. (26)

Dendritic cells are extremely efficient at both antigens presentation and induction of T cell response. These characteristics launched many attempts to build dendritic cells – based vaccines where dendritic cells are obtained from the patient’s blood, exposed to the tumor antigens, activated, and then transfused back into the patient’s blood. (27) This approach gives promising results in some patients with advanced cancers. However, there are still many obstacles in front of developing effective cancer vaccines, one of them that the selected tumor antigens should be expressed highly by the target cancer cells population and at the same time should be expressed at the lowest possible level by normal cells to avoid tissue toxicity of the cancer vaccine approach. (20)

Sipuleucel-T is the first dendritic cells – based cancer vaccine approved by US Food and Drug Administration (FDA) to treat stage IV prostate cancer in 2010. (29)

**Oncolytic Virus Therapy**

Oncolytic virus therapy represents a unique way to eliminate cancer cells. This approach includes local injection of biomedically -- engineered viruses that enter, replicate, and burst cancer cells. (30) Oncolytic viruses can promote anti-tumor response through two different mechanisms of action: cancer cells explosion by the viral infection itself and induction of general anti-tumor immunity. (21) Many of the cancer cells’ characteristics, such as uncontrolled proliferation, the resistance to apoptosis, and evading cellular growth suppressors
facilitate the selective oncolytic viral replication in cancer cells with minimal normal tissue toxicity. (3)

Talimogene laherparepvec (T-VEC) is the first oncolytic virus therapy approved by the FDA for the treatment of stage IV melanoma. (32) T-VEC is a modified herpes simplex virus (HSV) in which genes responsible for neuronal cells involvement are deleted and replaced by a specific nucleotides sequence for the GM-CSF cytokine expression. (33) Enhancing local secretion of GM-CSF can help in recruiting immune cells to the tumor area and promote their response against tumor cells. (34)

The limitations associated with oncolytic virus therapy are: the immunocompromised status in cancer patients which may limit the antitumor immunity mediated by the oncolytic viruses; the need to inject the oncolytic viruses into the tumor directly may limit its uses with difficulty accessible tumors and the sub-optimal level of efficacy showed in advanced metastatic tumors reveal the need to combine oncolytic viral approach with other therapies to achieve the desired outcome. (30)

Monoclonal Antibodies

Alemtuzumab is a monoclonal antibody that targets and attaches to CD52 antigen which expressed on lymphocyte cells. After attaching to CD52 alemtuzumab work as a marker and recruit immune cells to attack cancer cells. FDA approved alemtuzumab to treat special types of chronic lymphocytic leukemia (CLL). (35)

Trastuzumab is a monoclonal antibody that targets HER2 growth factor receptor that expressed heavily on a significant proportion of breast and gastric cancer cells. HER2 blockade will stop the uncontrolled proliferation and growth of these cancer cells. (36)

Ibritumomab tiuxetan is a monoclonal antibody attached to a radioactive particle that targets CD20 antigen expressed on B lymphocytes. By attaching to CD20 antigen, ibritumomab can bring the radioactive substances directly to the malignant cells. FDA approved ibritumomab to treat some types of refractory non-Hodgkin lymphoma. (37)

Brentuximab vedotin a monoclonal antibody attached to a powerful anti-cancer drug Monomethyl auristatin E (MMAE) that targets CD30 antigen expressed on B lymphocyte cells. By this approach, strong anti-cancer drug (MMAE) can be used without causing the serious side effects that occur when administered freely, not attached to a monoclonal antibody. FDA approved brentuximab vedotin to treat classical Hodgkin lymphoma and large B cell lymphoma. (38)

Blinatumomab is a combination of two different monoclonal antibodies that target two different antigens on two different cells at the same time, the first one target CD19 which expressed on B lymphocytes and the second one target CD3 which expressed on T cells. By attaching to these two antigens, blinatumomab can recruit and help T cells attack the malignant B cells. FDA approved blinatumomab to treat B-precursor acute lymphocytic leukemia b–ALL. (39)

Conclusion

Cancer treatment has depended for a long period of time on strategies and weapons that attack cancer cells directly. Cancer immunotherapy, the approach that harnesses the host’s immune system to fight cancer, is currently emerging as a novel cancer therapy. The most remarkable advancement has been made in cancer treatment in the last decades is the development of immune checkpoint inhibitors. The value of this scientific accomplishment is revealed by the fact that thousands of patients with advanced stages of cancer where the survival of patients is limited to within a few months have benefited already from the immune checkpoint blockade therapies. The rapid changes in cancer treatment approach apparently show that the therapies that target cancer cells selectively with minimal or no toxicity to the normal cells are the best and recommended. Therefore, cancer immunotherapy is expected to make a significant improvement on the efficacy and safety of cancer treatment and to be the frontline of cancer therapies in the years to come.

References


