

## The impact of Immunotherapy on Ovarian Cancer

Fayruz Omar Alsunbul;

Laboratory Specialist- MOH; Jeddah- KSA

---

**Abstract:** Ovarian cancer that estimated to be the top fifth leading cause of cancer death in women all over the world. Compelling evidence indicates that the immune response against ovarian cancer may play crucial role in controlling this problem. This review will discuss the recent clinical developments of selected immunotherapies for ovarian cancer. 68 articles had been reviewed carefully, our findings concluded that as the results of clinical trials of the discussed antibody based immunotherapies are inconsistent, it is still too early to conclude if these drugs will be incorporated into treatment regimens against ovarian cancer. Furthermore, their true potential may lie within being strategically employed in chemo-immunotherapy regimens.

**Key words:** Ovarian cancer, Immunotherapy, Immune response.

---

### I. Introduction

In the last few decades immunotherapy has become an important part of treating some types of cancers. One of these types is the ovarian cancer. Ovarian cancer, one of the deadliest cancers prevalent in women, is an unusual tumor found at the ovary, with the tumor originating from the modified pelvic mesothelium, which covers the ovarian surface and pelvic peritoneum.<sup>1</sup>

Immunotherapy, the recent approach to cancer therapy, is a type of cancer's treatment that increases the defense mechanism of the human body and helps to fight cancer. Antigen-specific immunotherapy is developed from the molecular identification of the human cancer-specific antigens. The standard approaches for the cancer treatment are radiation therapy, surgery, endocrine therapy and chemotherapy. Surgery and radiation are performed at the tumor site and the effects are precise. Oral and parenteral administration of endocrine and chemotherapy produces some systemic effects. The above four systems have adverse side effects, and the chances for the recurrence of the disease is very high.<sup>2</sup>

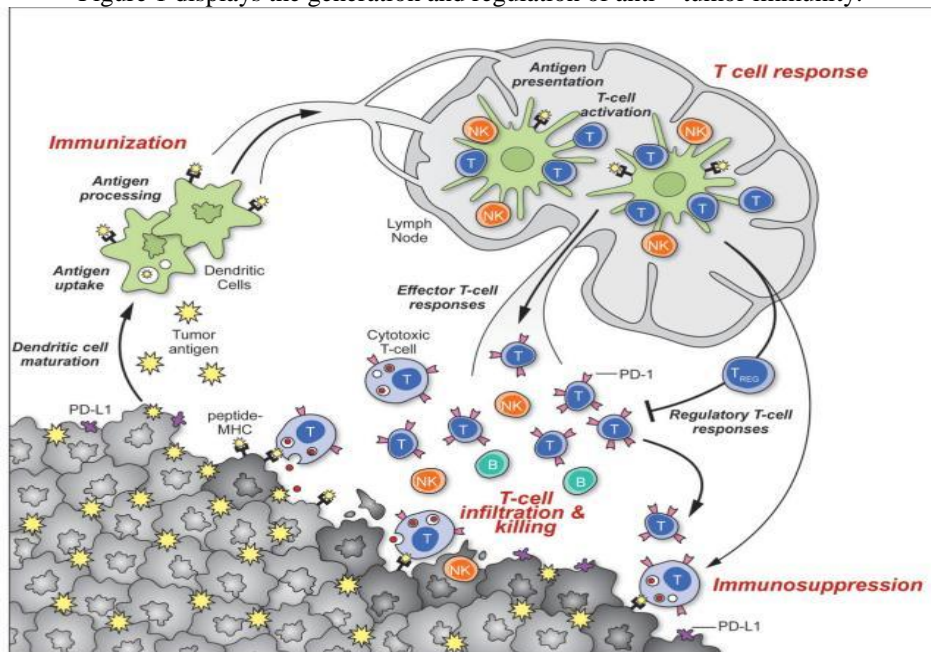
On the other hand, Liu et al. believe that immunotherapy does not have these adverse effects and is the most trusted one. The agents of immunotherapy are called as immunomodulators, with immunologic effectors such as mABs, cytokines and lymphocytes being used. The immune system is stimulated to destroy or reject the tumor from the body. The types of immunotherapy practiced for cancer are Dendritic cell-based immunotherapy, Adoptive T-cell therapy with tumor infiltrating lymphocytes, Vaccines and Engineering T cells.<sup>3</sup>

A number of defective proteins are produced by the cancer cells, if the immune system is not working properly in our body. Sometimes, high concentration of cancer proteins is produced and these abnormalities lead to an immune response, and that affects the cancer cells and the infected tissue. Stiff and Drakes reported that in many types of cancer, the immune system fails to identify and respond to the abnormalities, and the cancer cells are not attacked. Now the scientists are trying to find out a way to stimulate the immune system to recognize the cancer cells and destroy or inhibit the growth of cancer cells. During organ transplant, the patients receive some special drugs, to make the host to accept the donor organs. In organ transplant, there are chances for acceptance and rejection of the donor organs. If the immune system identifies the differences in the cells of the transplanted organ, then the immune system will attack the host cells and the rejection rate will be very high and destructive to the patient.<sup>4</sup>

The presence of a single foreign gene in the transplant may make the own immune system to identify as a cancer cell and destroy it. Chemotherapy is used in combination with the organ transplant, but the survival rate is not high. Many drugs are being tried to improve the survival rate and the current study also uses the drugs such as Folfirinox, gemcitabine, capecitabine, Nab-paclitaxel along with 5-FU chemoradiation and Apligenpantucel – L Immunotherapy. It was a Phase III study to assess the overall survival rate of pancreatic cancer patients with unresectable pancreatic cancer.<sup>5</sup>

Activation of the immune system for the treatment of cancer has come true in the clinical trials conducted by Dr. George Coukos and Dr. Takami Sato. Anti-CTLA4 antibody ipilimumab was found to show increased chance of survival in the metastatic melanoma patients after surgery.<sup>6</sup> Moreover, Interleukin-10 presence in the metastases and the correlation between the serum IL-10 level and disease progression plays an important role in preventing the cancer. IL-10 is found to down regulate the expression of Th1 cytokines and induces the T cell Regulatory responses.<sup>7</sup>

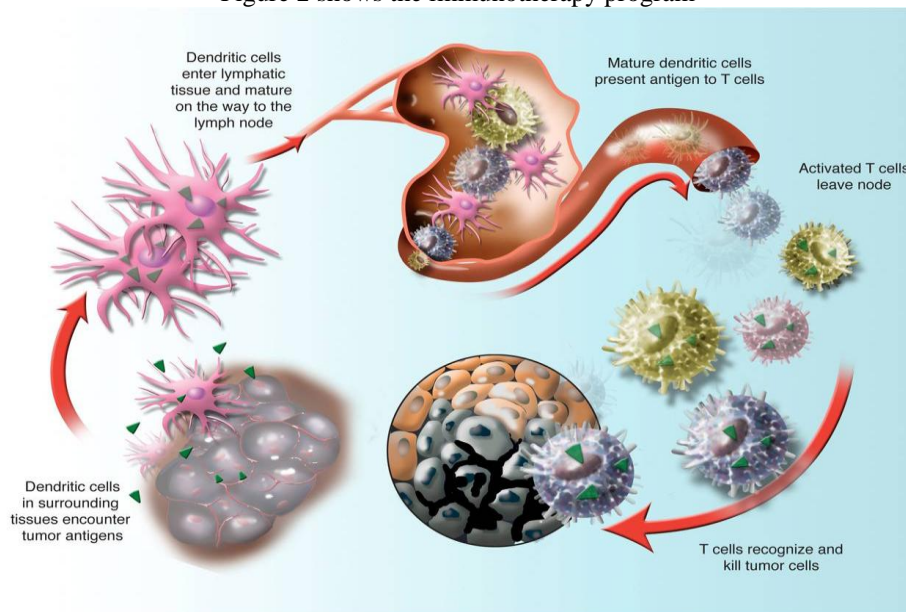
Figure 1 displays the generation and regulation of anti – tumor immunity.



## II. Ovarian cancer and Immune system:

Ovarian cancer, one of the deadliest cancers prevalent in women, is an unusual tumor found at the ovary, with the tumor originating from the modified pelvic mesothelium, which covers the ovarian surface and pelvic peritoneum. The pelvic peritoneum differentiates into many types of epithelial cells such as endocervical, endometrial, intestinal and Tubal cells and due to this reason, cancer originates at the ovary.<sup>8</sup> According to Stiff, and Drakes, the risk for ovarian cancer increases with age and it is most frequent after 40 years of age in women. Though the pathogenesis of epithelial ovarian cancer is not understood, it is believed that genetic damage caused by repeated ovulation leads to ovarian cancer.<sup>4</sup>

Figure 2 shows the immunotherapy program



Early detection of gynecological malignancy is not possible and is generally diagnosed, when it gets widely spread in the abdomen. Most of the patients are diagnosed at the advanced stage and these patients after the surgery will again relapse and require additional therapy. Many researches are going on to find an effective treatment method for the management of this recurrent disease, with majority of them have concluding that immunotherapeutic modulations are the best option.<sup>4</sup>

The first line defense against cancer is provided by the innate arm of the immune system. Monocytes and NK cells are involved in the elimination of cancer. Monocytes and NK cells are able to recognize and attack the down-regulated MHC class I cell expression. The treatment which uses the person's immune system for fighting against cancer is called as Cancer immunotherapy. This is performed by stimulating the person's own immune system for fighting against the cancer cells or by providing the immune system proteins, and thereby strengthening. Immune system is comprised of cells, tissues and organs that mediate the resistance to infections. Immune system prevents the growth of tumor, and many methods are used to treat the cancer by stimulating the immune system. There are two types of immunity: innate or natural immunity and adaptive or acquired immunity. The innate immunity is present in the healthy individuals and it prevents the entry of microbes and removes them from the body.<sup>9</sup>

Acquired immunity is the slow immunity that requires the differentiation of the lymphocytes to provide effective defense. The adaptive immune responses are classified as cell mediated and antibody mediated immune response. For the removal of intracellular organisms such as viruses, the T- cell mediated immunity is required. The same mechanism is used for the elimination of cancer cells. T-cell identifies the free antigen using the T-cell receptor and processes them into a tertiary oligopeptide, using the antigen presenting cells (APCs). These are then attached to the MHC complex I or II and helps in the clearance of the antigen. The cancer cells have altered DNA pattern and the functions are reordered and perturbed. These cancer cells are similar to the virus infected cells in their function. The immune system can identify these cancer cells and treat them in the same processes as that of virus infected cells.<sup>8</sup>

Ovarian cancer cells use many metabolic pathways to overcome the immune system. In the ovarian cancer, the immune system fails to work because of defective antigen presentation and lack of energy in the effector cells. Myeloid-derived suppressor cells (MDSCs) suppress the function of T-effector by producing arginase enzyme. Arginase reduces the L-arginine availability in the cell by reducing them into nitrates and carbons source. Macrophages produce around 50% of APCs inside the tumor. Thus macrophages are important in innate immunity and chronic inflammation. Ovarian tumor cells are involved in immune suppression and produces TNF- alpha, IL-6 and IL- 8.<sup>10</sup>

### **III. Treatment**

#### **Vaccine approaches**

The first cancer vaccine in human is attributed to William Coley in 1893. He observed that some patients with cancer benefited from bacterial infection resulting in tumour shrinkage. This prompted him to treat the patients with bacterial extracts. This novel observation led many to conclude that the immune system can recognize tumour-associated antigens. Administering the vaccine without knowing the antigens can still act on the tumors. The main reason for using the vaccines is to induce the already present anti-tumor immune responses. For the ovarian cancer, there are two phases I/II clinical trials for vaccine. The first clinical trial uses the protein extracted from the patient's frozen tumor. This protein is then injected into the dendritic manufacturing sites at the laboratory. The personalized vaccine is produced out of it and is administered along with bevacizumab to the patient at 2 week time interval for 5 times. This trial is in phase I only.<sup>11</sup>

The second trial uses the same frozen tumor protein and intra - dermally injected into the patient at small doses. The protein is combined with amplitgen and administered at two week interval for 5 times. Dendritic cell vaccines are very successful in treating cancer. Dendritic cells are the special immune cells that help the immune system to identify the cancer cells. After 40 years of research, it was concluded that dendritic cells are the nature's adjuvants and are the natural agents for antigen delivery. They have the ability to control immune tolerance and immunity.<sup>8</sup>

The cancer cells are broken into small pieces and provide them to the T cells. The T cells process the pieces and start the immune reaction against the cells that contain these antigens. These vaccines are patient specific vaccine and are made individually for each patient. This technique is quiet costly when compared to other anti-cancer approaches. Tumor cell vaccines are another type of cancer vaccine that is produced from the cancer cells which are removed during the surgery. The tumor cells are modified and mutated in the laboratory and is then injected back into the patient. These tumor cell vaccines are autologous in nature. Production of autologous vaccines is not easy.<sup>12</sup>

Vector-based vaccines use the delivery systems called vectors to deliver the cancer antigen to the target site. The vectors may be viruses, yeast cells, bacteria or other special structures. Vector- based vaccines are useful to deliver many cancer antigens at a time, to trigger the immune responses in the body and they are very less expensive than other immunotherapy techniques. The viral vectors are specific and they have their own advantages and disadvantages. The important viral vector is the pox virus.<sup>13</sup>

### **Monoclonal antibodies**

Monoclonal antibodies are the designed antibodies to target a specific antigen. Monoclonal antibodies can be produced in a large concentration at the lab and used for the treatment of ovarian cancer.<sup>2</sup>

### **Adoptive T cell therapy approach**

The transfer of genetically modified autologous tumor- reactive T cells into the ovarian tumor is called the Adoptive T cell therapy. These T cells carry the artificial programmed T cell receptors that target the tumor cells. This method is very useful for the patients with the advanced malignancies. In the current clinical trial, the patients who were initially given the vaccines are enrolled and the post – vaccine blood lymphocytes are harvested and activated in the culture and infused back into the patients. By providing altered T-cells, the patients are able to boost up the previous vaccine effects.<sup>14</sup>

### **Tumor infiltrating lymphocytes**

Anti- tumor immune responses are found in most of the patients with ovarian cancer at the diagnosis stage. Hence during the surgery, tumor reactive T cells are isolated from the patients. These T cells are then processed, stored and used for the immunotherapy. The combination of cytokine therapy and T cells will reduce the ovarian cancer in the patients. Genetically engineered T cell approach is performed by introducing the antigen specific artificial T cell receptor called as Chimeric antigen receptor or CAR. These CAR- engineered T cells links up with the tumor antigen and kills the tumor cells. The antigens used are mesothelin, folate receptor- alpha and NY-ESO-1. The alpha folate receptors are highly expressed in the ovarian cancer cells. The T-cell engineered alpha folate receptor dramatically reduces the cancer cells. This is still at the phase I trial.<sup>14</sup>

### **Immune checkpoint inhibitors**

Immune check points are the molecules of the immune system which need to be activated to start the immune response. Cancer cells uses these check points to escape from the immune system attack. The immune checkpoint protein plays an important role in limiting the potential damage caused to the T –cells on a foreign molecule entry. Immune check point inhibitors blocks these check points and thus lead to the damage of the T- cells. If the T-cell is produced by the tumor cells, then the use of immune checkpoint inhibitor will block the tumor cells and eliminate them. Drugs that target the immune system are Ipilimumab (an anti CTLA-4 antibody), nivolumab (an anti –PD-1 antibody), lambrolizumab and pidilizumab are some of the immune check point inhibitors for cancer. CTLA-4 is the check point molecule that is found in the T cells and it can be blocked by the drug Ipilimumab. The action of the drug increases the immune system response to cancer cells and leads to many side effects. PD-1/ PD-L1 are the other checkpoint molecules that are found on the T cells of the tumors. The drugs such as nivolumab act more specifically than Ipilimumab and shrink the cancer cells and eliminate them. They have lesser side effect than other types.<sup>15</sup>

### **Advantages of cancer immunotherapy according to Watson<sup>16</sup> as follow:**

- There are very few side effects in this treatment method.
- They kill only the tumor cells whereas in chemotherapy and radiation therapy all the cells are killed.
- Cancer immunotherapy creates specific immunity against the neoplastic cells and not against the normal cells.
- Synthetic peptide vaccines are very safe, reproducible and do not have oncogenic side effects.
- They can be engineered to defined conformational epitopes to act against tumor cells.
- Cancer vaccines are very specific, have less toxicity levels, do not have the circumvention of drug resistance.

## **IV. Conclusion**

Surgery and chemotherapy continue to be the important treatment method for ovarian cancer. The mortality rate is very high in these two treatment methods as ovarian cancer is diagnosed only at the advanced stage. In order to reduce the mortality, novel therapies like immunotherapy, vaccines were discovered and integrated into the current regimens. Immunotherapy uses parts of a person's immune system to fight against cancer. Immunotherapy includes treatments that work in different ways. Some boost the body's immune system in a very general way. Others help train the immune system to attack cancer cells specifically. Immunotherapy is safe, has less side effects and also the future management of ovarian cancer is easy. Monoclonal antibody- based immunotherapy, engineered T cells, immune check point inhibitors and tumor infiltrating lymphocytes are some of the immunotherapy methods used for the ovarian cancer treatment. Of these, monoclonal antibody- based immunotherapy offers potential benefits than the traditional methods and they are also found to be very specific in action have minimal side effects. There are very less cytotoxic side effects on the normal tissue than chemotherapy and radiation therapy.

### References

- [1]. Cheung NV. Chapter 32: Therapeutic antibodies and immunologic conjugates. In: Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, eds. *Abeloff's Clinical Oncology*. 2014; 5th ed. Philadelphia, Pa: Elsevier.
- [2]. Liu, B., Runowicz, C., Swede, H., Steven, R., and Li, Z.,. Ovarian Cancer Immunotherapy: Opportunities, Progresses and Challenges, *Journal of Hematology and Oncology*, 2010; 3(7): 45-5.
- [3]. Clinical Trails: Immunotherapy Study in Borderline Resectable or Locally Advanced Unresectable Pancreatic Cancer. 2014.; Available from <http://clinicaltrials.gov/show/NCT01836432> (accessed on May 12, 2015).
- [4]. Stiff, PJ., Czerlanis, C and Drakes, ML.,. Dendritic Cell Immunotherapy in Ovarian Cancer, *Expert Review of Anticancer Therapy*, 2013; 13(1): 43 – 53.
- [5]. Clinical Trails., Autologous: T cells combined with Autologous OC-DC Vaccine in Ovarian Cancer. 2013; Available from <http://clinicaltrials.gov/ct2/show/NCT01312376> (accessed on May 18, 2015).
- [6]. Mellman, I., Coukos, G and Dranoff, G., 2011. Cancer immunotherapy comes of age, *Nature*, Vol.480, No.7378, pp: 480-489.
- [7]. Sato, T., Terai, M., Tamura, Y., Alexeev, V., Mastrangelo, MJ and Selvan, SR.,. Interleukin 10 in the Tumor Microenvironment: a Target for Anticancer Immunotherapy, *Immunologic Research*, 2011; 51(2): 170-182.
- [8]. Mantovani, A and Sica, A.,. Macrophages, Innate Immunity and Cancer: Balance, Tolerance and Diversity. *Current Opinion in Immunology*, 2010; 22(2): 231 – 237.
- [9]. Topalian, SL.: MHC class II Restricted Tumor Antigens and the Role of CD4+ T Cells in Cancer Immunotherapy, *Current Opinion in Immunology*, 1994; 6(5): 741 – 745.
- [10]. Watson, JM., Sensintaffar, JL., Berek, JS and Martinez-Maza: Constitutive Production of Interleukin 6 by Ovarian Cancer Cell Lines and by Primary ovarian Tumor cultures, *The Journal of Cancer Research*, 1990; 50(1): 69-59.
- [11]. Clinical Trails.: A Clinical Trial of Autologous Oxidized Tumor Cell Lysate Vaccine for Recurrent Ovarian, Fallopian Tube or Primary Peritoneal Cancer. 2012; Available from <http://clinicaltrials.gov/ct2/show/NCT01312389?term=UPCC+29810&rank=1> (accessed on June 12, 2015).
- [12]. Palucka, K and Banchereau, J: Cancer immunotherapy via Dendritic Cells, *Nature reviews: Cancer*, 2012; 12(4): 265- 277.
- [13]. Larocca, C and Schlom, J.: Viral Vector- based Therapeutic Cancer Vaccines, *NIHPA Manuscripts*, 2011; 17(5): 359 -371.
- [14]. UPHS.upenn.edu., 2014. Penn Ovarian Cancer Research Center Immunotherapy Program. Available from
- [15]. [http://www.uphs.upenn.edu/obgyn/research/ovarian\\_clinical.htm](http://www.uphs.upenn.edu/obgyn/research/ovarian_clinical.htm) (accessed on Nov. 2nd, 2015).
- [16]. McDermott, DF and Atkins, MB.,. Pd-1 as a Potential Target in Cancer Therapy, *Cancer Medicine*, 2013; 2(5): 662 – 673.
- [17]. Mabuchi, S., Morishique, K and Kimura, T., 2010. Use of Monoclonal Antibodies in the Treatment of Ovarian Cancer, *Current Opinion in Obstetrics and Gynecology*, vol.22, No.1, pp: 3 – 8.