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Radiotherapy and Immmun Responce is the Radiotherapy Vaccine? Good News?

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Öz

Radyoterapi (RT) immün yanıtı aktive etmektedir. Bundan dolayı "radyoterapi aşımıdır" sorusunu tartışmak gerekmektedir. RT, immün yanıtı artırıyorsa, hücrelerdeki RT etkileri, hücre yüzeyi antijeni, immün kontrol noktaları ve bunların inhibisyonu hakkında daha fazla bilgi edinmeliyiz (ICI; CTLA4, PD1, PDL1 inhibisyonu). Bu derlemede, radyoterapinin ve biyolojik etkilerinin immun cevabı aktive etmede ki rolü, radyoterapi dozu, radyoterapi zamanlaması ve immun kontrol noktaları baskılayıcılarının yan etkileri tartışılacaktır.**Anahtar Kelimeler:** Radyoterapi, İmmun Yanıt, İmmun Kontrol Noktaları.

Abstract

Radiotherapy (RT) activates immun responce. Because of this we must discuss the question of "is the radiotherapy vaccine". If RT increases the immun response we must learn some more about the RT effects on the cells, cell surface antigene, immun checkpoints and their inhibition (ICI; CTLA4, PD1, PDL1 inhibition). In this review it will be discussed the role of the radiotherapy and biologic effects of the radiotherapy to activate the immun responce, radiotherapy dose, radiotherapy timing and the side effects of immun checkpoints inhibitors.
Keywords: Radiotherapy, İmmun Response, İmmun Checkpoints.

1.Logın

In the multimodally approch we are fighting against cancer with Radiotherapy (RT), Chemotherapy (CT), Surgery (S) and Immunotherapy (IT). There are new informations about to use IT and RT. In this review will be discussed the role of radiotherapy for immun response.

As seen on the Figure 1 the human breast cancer cell line MDA-MB-231 are growing easy on biocompatibility of vertically aligned multi-walled carbon nanotube scaffolds [1]. There is smilar cancer growth in human body and our immun system is trying to inhibit the cancer cells.

In tumor microenvironment there are many cells; such as normal epithelial cells, mesenchymal cells, endothelial cells, macrophage (M), tumor assosiated macrophage (TAM), fibroblast (F), cancer associated fibroblast (CAF), dentritic cells (DS), antigen presenting cells (APC), T-B lymphocytes, cancer cells and many dead cells of cancer cells and normal cells (Figure 2).

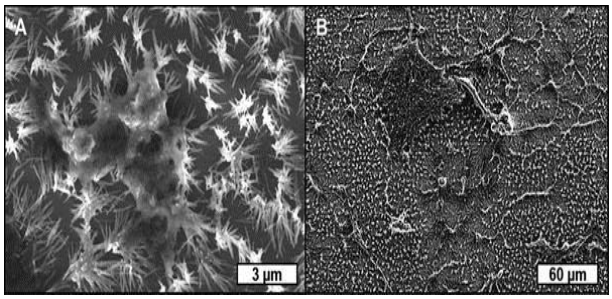

Figure 1: Biocompatibility of vertically aligned multi-walled carbon nanotube scaffolds for human breast cancer cell line MDA-MB-231

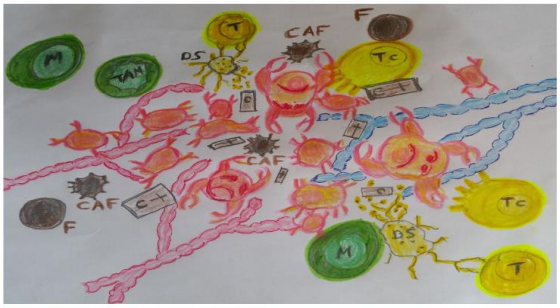

Figure 2: Cancer microenvironment

There are many dead tissues and necrotic secretions in the carcinoma microenvironment. These increase with treatments and may protects cancer. Inflammatory response increases pressure and may protects cancer. M2, TAM, CAF, peristicle, collagen tissue may protect cancer.

During RT planning usually we include in the treatment volume primary gross tumor volume + clinical target volume + lymph nodes (Figure 3) [2]. But if we want a good immun responce we need cancer antigens and lymphatics. Because of this we must discuss to save regional lymphatics and to give RT before S.

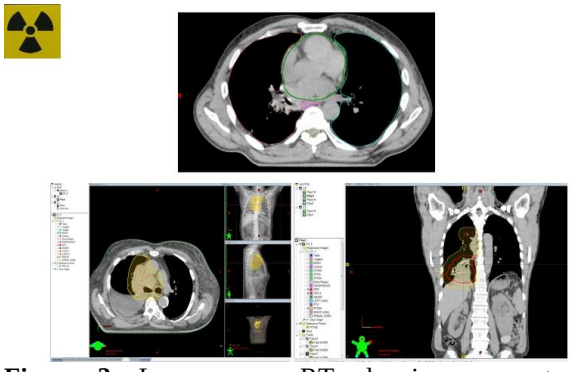

Figure 3: Lung cancer RT planning, gross tumor volume + clinical target volume + lymph nodes

In radiation biology, we had 4R [3]; Repair, Redistribution, Reoxygenation (but RT may cause hypoxia, this may bad news and needs Anti VGF), Repopulation (this may bad news because RT may stimulates cancer growth) and 5R; Radioresistant/Radiosensitive tissue or cancer. Now we have 6R; IMMUN REJEKTION, this may be a good news? Because Radiotherapy activates immun response (Figure 4).

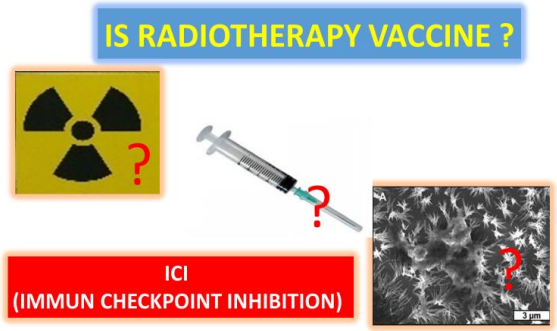

Figure 4: Is the radiotherapy vaccine?

In oncology practice there are some vaccines, such as; Oncolytic virus, BCG [4]. Also;
Sipuleucel-T is a DC-based vaccine containing GM-CSF. White cells (DS, Mo-Ma, B cell) are taken from the patient's with apheresis and transferred to the fabrication, where meeting with recombinant antigen-Sipuleucel-T / Provenge, Dendritic cells mature with GM-CSF and the T cell is matured and activated, then is given back from the vein the patient. This is an active cell immunotherapy in castration-resistant prostate cancer, and
Cimavax-EGF (CUBA): If menejitis bacteria inoculated to patient body, produces antibodies against EGF. The EGF amount is reduced [5, 6]. Cancer can not progress and can not metastasis. Another non-vaccine treatment also against the EGF receptor as TKI. Including to above;
Is the radiotherapy vaccine? If RT increases the immun response we must learn some more about immun checkpoint inhibition (ICI; CTLA4, PD1, PDL1 inhibition) [7].

There are some molecules called Major Histocompatibility Antigene (MHC) or Human leukocyte Antigene (HLA) for immun activation after RT; MHC 1 (HLA- A, B, C) cell surface molecules is to deliver intracytoplasmic antigens such of viruses and tumor antigens presented to CD8 + cytotoxic T cells by cell. MHC 2 (HLA-DP, DR, DQ) are the cell surface molecules, which has been taken by bacterial endocytosis to presented to CD4 + helper T (Figure 5-6) [8].

Th1 cells provide the cellular immunity of the person with interferon gamma (IFN-γ), interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF-alpha). IL-2 specifically proliferates cytotoxic T-cells and activates IL-2 NK-cells. Also the TNF-alpha stimulates T-cells and NK-cells to attack the tumor. INF-γ helps HLA-expression and enhances antigen presentation to effector T-cells [7-9].

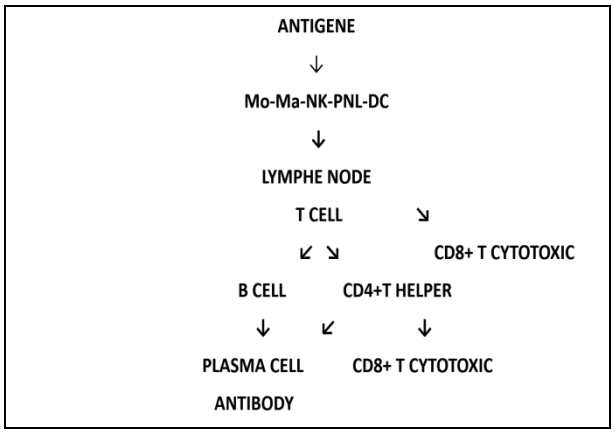

Figure 5: Immun activation after RT

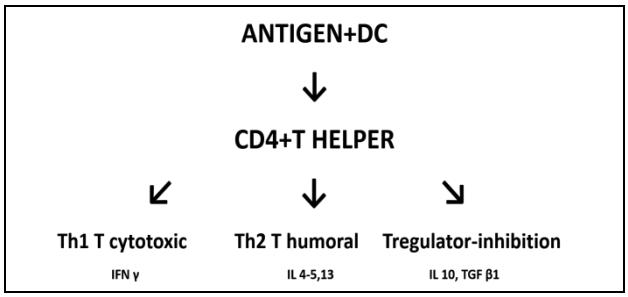

Figure 6: CD4 + T helper

Th2-cells secrete more IL-4, IL-5 and IL-10 than Th1-cells and Th2-cells support the immune response with antibody production. IL-4 stimulates B-cells through IgE. IL-10 contributes to the formation of B-cells, monocytes and granulocytes [7-9].

When we give RT to cancer microenvironment we may will see many reactions [10-15];

1. Tumor antigens (MHC1/2) excrete to extra cellular matrix. Macrophages and dendritic cells (Dentritic-Cell DC) take them, go to the lymph glands, and these antigens present to the effector T cells and activate T cytotoxic cells (Tc) (CD8 + T lymphocytes).

2. DNA binding protein HMGB1 (High Mobility protein Group Box 1) Increases with radiation. The HMGB1 protein release to extra cellular space. HMGB1 is TLR4-associated dendritic cell activator.

3. ATP (Adenosine triphosphate) appears after RT damage, activate immun responce.

4. When DNA is damaged, ATM (Anti telengectase mutated protein) comes out.

5. NKG2D (Natural Killer group 2D) ligands are increased. NK and active CD8 + T cells attack these ligands on cancer. Also the activeted Tc attacks to metaplasia and metastasis.

6. From the endoplasmic reticulum, Calreticulin appears on the tumor surface. Calreticulin pre-apoptotic is released and it is the message to "eat me" in cell translocation.

7. Uric acid and Nitric oxide increases are released into the tumor space and cancer is eliminated by macrophages

8. HSP (heat shock protein) increases. They stimulate the Dentritic Cell (DC). DC stimulates CD8 + Tc.

9. Ceramide is present in the vascular endothelial membrane and also in all membranes. Ceramide is a member of the siphingolipid family, leads to apoptosis. It also helps in immunotherapy (IT) by providing Dentritic Cell maturation with MHC1 increase.

10. ICAM1 (CD54): Intra Celluler Adhesion Molecul/Inter Celluler Adhesion Molecul. After RT lymhatic endotelial cell adhession increased to keep the immun cells for immun response

11. Fas (CD95): First Apoptosis Signal (Apo1 or tumor necrosis factor receptor superfamily member 6) binds to the protein ligand (FasL), resulting in apoptosis signaling from the nucleus leading to cancer cell death.

12. The formation of ROS (reactive oxygen substrate) also kills cancer.

13. Radiation kills cancer directly but also activate immune responses through the Stimulator of Interferon Genes (STING)-mediated DNA-sensing pathway.

14. After RT, IFN gamma released against cancer to increases immune cell migration to the tumor site, has anti- proliferative and antiangiogenic effects, cytotoxic effect on cancer. IFN causes apoptosis in the cancer. Also IFN gamma / IL-12 are secreted by tumor-infiltrating monocysts / macrophages / DCs and these activate the Natural Killer (NK) cells and these helps to open holes in the cell with perforin granule enzyme and por forming cytolytic protein. Por caspase or Fas-L caspase stimulus kill the cancer.

2. Abscopal Effect (Ab: remote, away from. Scopes: target, purpose, aim, scope); Divided into two; The near abscopal effect (bystander effect, audience effect) and the remote abscopal effect [16-18].

Abscopal effect cannot be obtained in non-T cells rats. After RT, close and distant cancer cells may shrink and disappear. Because the antigens released by RT-receiving cells are taken up by Macrophages and DCs, and in the lymph node these antigens recognized by the effector T-cell and the activated immune system kills close and distant cancer cells. CD8 + Tc and Type1 Interferon are increase. As seen on the figure 7, the left lower metastatic lesion has disappeared after RT to only the left hiler primary and mediastinal lymph nodes because of the abscopal effect of RT [19].

BUT, if proliferating cancers and metastases mutate, it may be a new antigenic construct and we can not see abscopal effect. Cancer cells are heterogeneous and each cancer cell has similar and dissimilar antigens. For this reason, the immune response may not be against every cell. Also it is very importantly that normal person has immun check points (ICP) to protect its self from over immun attack to from auto immun diseases. If ICP works in cancer patients our immun system can not attact to kill the cancer cells. Because of these, we must discuss how the ICP works and we need ICP inhibition to fight against cancer (Figure 8).

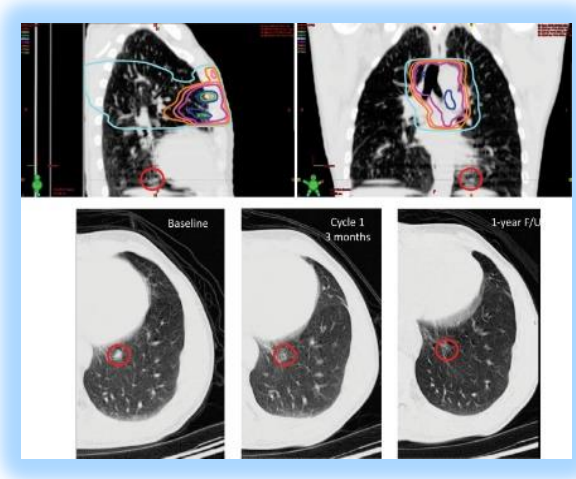

Figure 7: Abscopal effect [19]

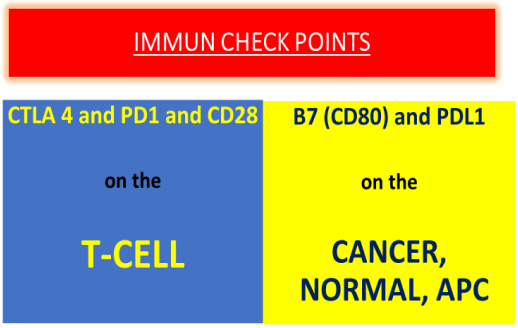

Figure 8: Immun Check Points (ICP)

There are naturel immunocompromised checkpoints against autoimmunization (CTLA4, PD1, PDL1) and block the immune response, otherwise the body will accept its normal cells as foreign.

CTLA4 (Cytotoxic T Lymphocyt Associated antigen 4) immunity checkpoint prevents self-attack in normal human and normal tissues. Protects us and prevents autoimmune disease. CTLA4 is on T lymphocyte, and if B7 (B; Bursa of Fabricius was used to identify unknown B cell antigens and ligands in studies previously performed with monoclonal antibodies. Now this terminology is also used in APC and DC. B7 peripheral membrane protein; T cell surface co stimulatory molecule) are on the normal and APC or cancer cells. If CTLA4 and B7 binds; T lymphocyte can not attack.
The MHC antigen stimulates APC and DC receptors, also at the same time directly stimulates on T cell receptors. CD28 (Cluster of Differentiation 28) in the T cell communicates with B7 in APC provides immun activation. When this activation reaches a certain level, CTLA4 which is on the active T cell binds to the B7 ligands on DS or APC in order to avoid autoimmune attack, and immuno-suppression. If anti-CTLA4 is given, B7 continuously stimulates the T cell and increases the immune response.
B7 and CTLA4 receptor interaction between tumor cell and APC then inactivates T cell. If Anti CTLA4 is given, T cell becomes active. Anti CTLA4 T blocks CTLA4 on the cell. The APC stimulus continues at T and T attacks the cancer. If anti-CTLA4 (Ipilimumab) is given, B7 can not bind to CTLA4 in dendritic cells or in APC, and the attack continues (Figure 9). Also, APC (antigen presenting cell) stimulation continues on T-lymphocytes, the attack is exacerbated, but it is also necessary to pay careful attention to the attacking of normal tissues which cause hazards and side effects.

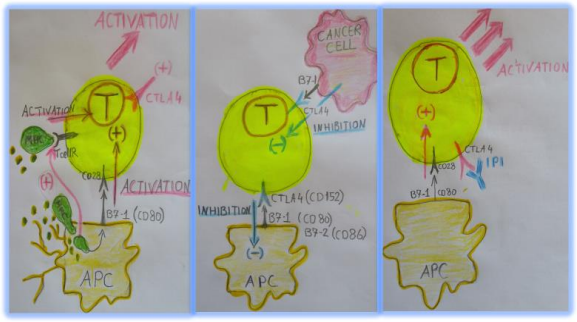

Figure 9: Activation and inhibition with B7, CD28 and CTLA4 interactions

The PD1 is on T CELL and PDL1 is on NORMAL and APC and cancer cells. When RT is given, PD1 and PDL1 are overexpressed. If contact on T cell PD1+PDL1 on the tumor cell/normal/APC cell deactivates the immun T cell. ICI antibodies (anti-PD, anti-PDL1) are continue to activate immune response against cancer (Figure 10).

PD1 is present in activated T cells and must bind to PDL1 to suppress T cell immunity. PDL1-2 is present not only in antigen presenting cells but also in cancer cells, and T cell inhibition occurs when the PDL1 ligand of APC or tumor cell meets with PD1. Therefore, if anti PDL1 is given, PDL1 and PD1 will not meet, APC will not be suppressed, and it will be continuously stimulates APC and the killer cell will attack to cancer in active state. Cancer can not prevents T cell attacks.

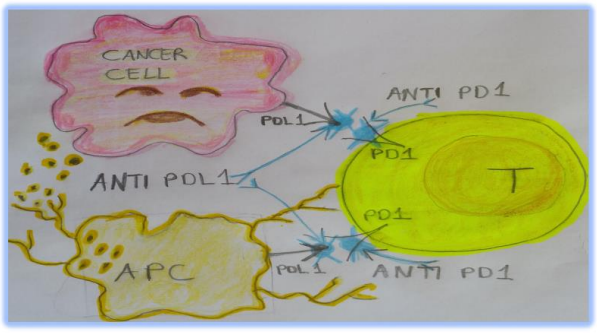

Figure 10: PD1/PDL1 interactions and anti PD1/anti PDL1

Anti PDL1 closes the PDL in the cancer and in APC. The PD1 in the cancer and in the APC can not contact with PDL and the T attack continues. if we give an ICI,

auto-immunity is exacerbated and side effect increases. If B7 is blocked, the CD28 stimulus is turned off and immun stimulation is reduced.

In the KEYNOTE 001 study; after other therapy in advanced or methastatic non small cell lung cancer for any RT + Anti PD1, the mean overall survival was 10.7 months versus for only Anti PD1 was 5.3 months. For any extra cranial RT+ Anti PD1 the mean overall survival was 11.6 months versus only Anti PD1 was 5.3 months. The Pulmoner toxicity was %63 who took lung RT versus %40 who did not take lung RT [20].

In the PASIFIC PHASE 3 study; the local advanced stage III NSCLC patients who had received KTRT, were treated with 12 months PDL1 block and the progression free survival was 16.8 months versus 5.6 months for placebo [21].

Sıde Effects Of Icı+Rt [22, 23]: The most common autoimmune side effect is on the skin, like vitiligo, but G3-4 is less. In addition, the gastroenteritis, nausea, vomiting, reduced appetite, fatigue can be seen. Also colitis, pneumonia, hepatitis, nephritis may occur. Attacks on the endocrine system can lead to hypothyroidism, thyroiditis, hypophysitis, colitis, pneumonia, these are threating the life.

CTLA4 is the first and early control point and early side effects can be expected (dermatitis, vitiligo, gastroenteritis, hepatitis, endocrinopathy, thyroid dysfunction). PD1 / PDL1 is the second control point and late side effects can be expected. (Lung pneumonia in the late period).

Rt Dose and Tımıng [7-11, 24]: Low-dose RT is insufficient to activate the immune system. Very high doses completely eliminate the anti-tumor effect of the immunizing system. In addition, excessive antigen presentation may also exert a stifling effect on the immune response. Because of this the dose must be stimulate cytotoxic cells while decreasing T regulatory cells.

Low doses below 2Gy can not kill cells. It is more likely to induce macrophage stimulation, where the macrophages (M2/ TAM) provide anti-inflammatory effects and thus impair the immune response. At doses above 2 Gy, cancer cell surface antigens (MHC1, ICAM, Fas) are exaggerated from the cell.

In X-Ray RT, the input and output doses act on normal tissues and also suppress the immunological response at the around and within the cancer. Proton is better in this respect [25].

The hypo fractionated RT with stereotactic RT (SBRT) with 1x20Gy, 3x8Gy, 5x6Gy is recommended (3 or 5 fractions are preferred to 1 fraction. The best is 3x8Gy) such as 3x8Gy or 5x6Gy + anti-CTLA4 (3 mg/kg every 1-3 weeks for 4 doses) instead of a single dose of 1x20Gy or 1x15Gy, 5x3Gy, 3x5Gy, 2x7.5Gy (The best is 2x7.5Gy).

If ICI is given too long before RT, the RT given later will destroy existing cytotoxic T lymphocytes and the response will diminish. If immunotherapy is given just prior to RT, there is an immunologically prepared environment and RT effect is increased. If RT is given first, the cells that are found to recognize and to kill the tumor cells die and the immune response can only be achieved by introducing immunogenic cells from the outside. The best is given; just before RT, or during RT, or immediately after RT.

3. Conclusion; It is clear that the RT activates the immune response. After RT there are many changes in the cancer cell or around the tumor microenvironment and these activate the immune response. But the cells have some immune check points to protect auto immune disease after a certain level of immune activation. If we use the ICI with RT we may see better immune response but we may pay attention to the side effects of these application.

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