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Combination of radiotherapy and immunotherapy for drug-resistant TNBC

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Abstract. Triple-negative breast cancer (TNBC) is a specific subtype, the most lethal and with the worst prognosis, and is prone to develop drug resistance during advanced chemotherapy. The combined application of radiotherapy and immunotherapy has gradually entered the public eye. The PD-L1 / PD-1 immune checkpoint inhibitors can enhance the local effect of radiotherapy and relieve the immunosuppressive effect in tumor patients, and the up-regulation of PD-L1 expression caused by radiotherapy also helps the checkpoint inhibitors to play a stronger effect. More patients with TNBC can gain a higher benefit from this.

Keywords: TNBC, immunotherapy, radiotherapy.

1. Background

1.1. TNBC

In recent years, breast cancer has become the most common cancer type which was according to the 2020 WHO cancer study data. Among them, triple-negative breast cancer (TNBC) is a special subtype, which is also the most lethal and has the worst prognosis, accounting for 15% to 20% of all breast cancer types [1]. The pathological characteristics of triple-negative breast cancer are estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2) are all negative [2], Its clinical features are poor differentiation and highly invasive, prone to early metastasis and recurrence, and poor prognosis. Because of its expression as triple negative, both traditional endocrine therapy and molecular targeted therapy are not sensitive. In clinical practice, chemotherapy is the standard treatment for advanced TNBC, but its therapeutic effect is still not ideal. Patients often show chemotherapy resistance at the early stage, which cannot prolong their survival. Therefore, it is urgent to find new treatments for TNBC patients.

Drug resistance of TNBC is one of the main reasons for the low benefit of patients undergoing chemotherapy, and the ATP-binding cassette (ABC) transporter is one of the main mechanisms. ABC exists on the cell membrane and uses ATP water to transport different kinds of anticancer drugs out of the cell, weakening the therapeutic effect, which is closely related to the generation of drug resistance [3]. Among all the subtypes of breast cancer, TNBC, the expression of ABC in the patient was significantly increased. While receiving chemotherapy, anticancer drugs also increased the expression of transporters, making the patients develop drug resistance very early.

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As we are constantly exploring the treatment of drug-resistant TNBC, radiotherapy, and immunotherapy have gradually come into view. Many studies have shown that local radiation therapy with the appropriate radiation dose can activate the body's systemic immune function, and its effect is more obvious when applied in combination with immunotherapy.

1.2. Immune mechanism

The immune system in TNBC patients has a dual effect on the tumor, which can simultaneously cause the anti-tumor immune effect to kill the tumor and induce the tumor to form immune tolerance. The role of the immune system can be divided into three processes: clearance, balance, and escape [4]. Specific and non-specific immunity jointly clear the tumor cells, and the tumor cells that fail to be completely killed in this process undergo escape and will enter the immune equilibrium stage, which then produces immune tolerance. Immune escape refers to escape the monitoring of the body so that tumor cells are protected from the attack of the immune system, such as down-regulating MHC I molecules and affecting the immune response of T cells. At the same time, an inhibitory tumor microenvironment (TME) is established in the body, including immunosuppressive cells, with obvious immune escape, making the tumor continue to grow and invade the metastasis [5].

2. Radiotherapy

The main treatments for tumors are chemotherapy, radiotherapy, and targeted therapy. It is currently believed that radiation therapy can directly kill the primary tumor by inducing single-strand breaks, double-strand DNA damage, chromosomal aberrations, and mismatch repair [6]. Recent studies have found that the appropriate radiation dose and compartmentalization can increase the tumor-infiltrating immune cells, reverse the inhibitory tumor microenvironment, generate the immune activation effect in the irradiated area, and then kill the tumor cells. The body's immune response stimulated by radiation therapy promotes mature DCs (dendritic cells to tumor tissue, identify and present tumor antigen, activate T lymphocytes and initiate anti-tumor immune response [7, 8]; Meanwhile, increase chemokine and vascular adhesion molecules to promote the migration of T cells to tumor tissue. Local radiotherapy can also cause a remote effect (abscopal effect), which reduces the local tumor lesion and the tumor lesion outside the target area, which is related to the infiltration of immune cells into the tumor microenvironment promoted by radiotherapy [9]. In addition to immune activation, radiotherapy can also induce immunosuppressive effects in the body [10].

Immunosuppressive molecules are up-regulated and the inhibitory tumor microenvironment is strongly expressed, hindering the specific immune responses of T cells [11]. For example, radiation leads to the up-regulation of programmed death ligand 1 (PD-L1)， which is on the surface of tumor cells, combined with programmed death receptor 1 (PD-1) expressed on the surface of T cells. Their combination can inhibit the effects of T cells to reduce anti-cancer treatments. Tumor cells damaged by radiotherapy recruit regulatory T cells (Treg), macrophages, marrow-like inhibitory cells (MDSC), and other immunosuppressive cells to reduce the body's immunity and promote the growth, metastasis, and spread of tumor cells.

The mechanism and effect of treating TNBC with radiotherapy have dual effects. Different irradiation doses, segmentation, and irradiation times have different effects on the results, suitable for radiotherapy can increase tumor local T cell infiltration, reduce the content of Treg, tumor tissue activated immune and immune suppression to achieve a good balance, achieve the purpose of anti-cancer, prolong the survival of patients.

3. Immunization therapy

Immune checkpoint, which refers to the programmed death receptors and their corresponding ligands. The PD-1 / PD-L1 interaction in normal tissue prevents tissue damage and limits the inflammatory response mediated by T cells and other components of the immune system during infection. TNBC, in the patient, tumor cells express PD-L1 which combined with PD-1 on T cells, weaken their immune function to escape the recognition and elimination of T cells [13]. The tumor cells of such breast

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cancer subtypes of TNBC express more PD-L1 , which is also responsible for their poor prognosis [14]. Therefore, blocking the mutual effect between PD-1 and PD-L1 could enhance the aggression of T cell-mediated specific immunity and kill tumor cells.

The FDA, the EMA, and other agencies have approved the treatment of immune checkpoint inhibitors (ICIs) in tumors. At present, Durvalumab and Atezolizumab have been approved for the treatment of cancer in China. They all belong to PD-L1 immune checkpoint inhibitors, while Nivolumab, Pembrolizumab, and Tislelizumab all belong to PD-1 inhibitors. These drugs can inhibit the growth of tumors, reduce the volume of tumors, and even appear complete regression, prolong the survival of cancer patients, and improve the quality of life of patients. Compared with radiotherapy and chemotherapy, the toxic effect produced by this immunotherapy is significantly reduced, which is a highly efficient new anti-cancer method, and has become a research hotspot of different anti-cancer therapies in recent years.

PD-L1 / PD-1 immune checkpoint inhibitors block PD-L1/PD-1, "rescue" T cells, to play an anti-cancer immune response, destroy the role of highly immunosuppressive cells, and restore the body's anti-tumor immunity. Radiation therapy can activate or suppress the immune response. PD-L 1 / PD-1 immune checkpoint inhibitors reduce the immunosuppressive effects of radiotherapy and restore the T cell-mediated anti-tumor immune response [15]; the combination reduces the radiation dose and reduces the side effects of radiotherapy, such as skin damage, nausea, and vomiting, to benefit cancer patients.

4. A combination of radiotherapy and immunotherapy

The combination of radiotherapy and immunotherapy is theoretically mutually beneficial. PD-L1 / PD-1 immune checkpoint inhibitors can improve the local effect of radiotherapy and relieve the immunosuppressive effect, and the up-regulation of PD-L1 expression caused by radiotherapy also helps the checkpoint inhibitors to exert a stronger effect.

A phase 2 clinical study evaluated the effectiveness and practicality of Pembrolizumab + radiotherapy (RT) in mTNBC patients not screened for PD-L1. Seventeen patients had been selected to participate the experiment , with Pembrolizumab added to an RT irradiation which had a specific dose. The ORR of this experiment was 17. 6%. Among the patients, 3 of them were complete responses (CRs), 13 people were progressive diseases and 1 person was stable disease . Before the end of treatment, 8 of them died because of disease progression. Of the nine female patients evaluated at week 13, three achieved CR, with a 100% reduction in tumor volume. The most common side effects of this trial were dermatitis; adverse events due to Pembrolizumab were lymphopenia, fatigue, and infection [16]. The combined anticancer effect of Pembrolizumab + RT is better than a single method of treatment, and it is additionally clearly effectual in the "king of breast cancer" TNBC. However, if TNBC patients can be screened for PD-L1, better therapeutic benefits may be obtained.

A study about brain metastasis in breast cancer demonstrated the potential of radiotherapy to increase the sensitivity of breast cancer brain metastasis to immune checkpoint inhibitors. Murine breast cancer has distant metastases, brain metastases, immune cells such as T cells, and tumor cells expressing PD-L1, which can be treated by PD-L1 / PD-1 pathway blockade. The combination of classical fractionated whole brain radiotherapy (WBRT) and PD-1 immune checkpoint inhibitor up-regulates the proportion of T cells and infiltrates tumor tissue. At the same time, the application of radiotherapy suppresses the compensatory inhibitory response of lymphocytes induced by PD-1 immune checkpoint inhibitor anticancer therapy [17]. Compared with the separate application of radiotherapy or immunotherapy, the survival time of mice was significantly prolonged, and the safety and therapeutic benefits were also clearly shown.

5. Boundedness

Immune checkpoint inhibitors are a hot topic in anti-cancer therapy, and the efficacy and safety of such drugs are also obvious, but immunotherapy still has many limitations. Before and after treatment, PD-L1 expression levels will change and even turn negative [18, 19]. When tumor biopsy or PD-L1

screening is desired, the results will also be affected by many factors, such as the difference between the primary focus and the metastatic focus, the different preservation methods of the examination biopsy, and so on [20-22].

In practical clinical application, PD-1 / PD-L1 immune checkpoint inhibitors still have many problems to be solved, for example, when the systemic injection of immune checkpoint inhibitors will cause serious toxic side effects on many tissues and organs, fever, edema, liver toxicity, etc. ; and immune checkpoint inhibitors are not suitable treatments for all patients, often appear ineffective [23]. Different tumor micro-environments have unique immunosuppressive mechanisms, requiring the selection of new methods and injected doses based on the different immune cell compositions. And the high price is expensive and will bring an economic burden to patients. The efficacy of radiotherapy also varies from person to person. Due to personal health status and physical conditions, the effects and side effects after treatment are not the same, and many patients have little effect or cannot tolerate it. Radiation therapy may be such as dermatitis, tissue damage at the irradiation site, or permanent organ damage, and these side effects can limit daily life and even reduce the quality of life. Therefore, how to select the appropriate immune checkpoint inhibitors, the sequence and timing of injection, the injection dose; the irradiation method, the segmentation method, and the irradiation dose of radiation therapy are all facing the current problems.

6. Conclusion

Existing experimental results prove that the combination of radiotherapy and immunotherapy is safe and effective, better than a single treatment, and patients can benefit from it. Up to now, many prospective research trials on triple-negative breast cancer are still ongoing, such as NCT03464942, NCT03004183, etc, using different segmentation methods and irradiation doses, combined with different kinds of ICIs for therapy of patients with certain conditions. However, the results of these experiments cannot be evaluated at present, and the factors are different among the trials, so the influencing factors should be excluded to further explore the specific mechanism and benefits of the combination of radiotherapy and immunotherapy in TNBC.

7. Look into the distance

Immunotherapy has made many remarkable achievements in the practice of TNBC treatment and has become an emerging hot spot at present. The therapy of resistant TNBC is safe and effective, but how to enhance the response rate of combination therapy, to achieve the purpose of controlling and even curing the tumor and maintain the quality of patients' life is still our facing challenges. TNBC is the most aggressive subtype of breast cancer, characterized by low survival, a high rate of distant metastasis, few effective treatments, and poor prognosis. Recent clinical studies have combined TNBC to overcome the early emergence of resistance by traditional chemotherapeutic means. Looking forward, the clinical research of drug resistance TNBC will find new and more suitable treatments, individualized treatment regimens, precise patient stratification, and combination regimen, so that more patients can benefit from combination therapy.

References

[1] Dent R, Trudeau M，Pritchard KI，et al. Triple-negative breast cancer: clinical features and patterns of recurrence [J] . Clin Cancer Res2007，13(15 Pt 1) : 4429-4434

[2] Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. NCCN Guidelines Insights: Breast Cancer, Version 1. 2017. J Natl Compr Canc Netw. 2017;15:433–451. [PubMed: 28404755]

[3] Nedeljković M, Damjanović A. Mechanisms of Chemotherapy Resistance in Triple-Negative Breast Cancer-How We Can Rise to the Challenge. Cells. 2019 Aug 22;8(9):957. doi: 10. 3390/cells8090957. PMID: 31443516; PMCID: PMC6770896.

[4] Xu Yunyun, Hong Mei, Li Guixiang. Effect of radiotherapy on the mechanism of anti-tumor immune effects in the body [J]. Modern Oncology, 2016, 24 (24): 4023-4025.

[5] Emens LA. Breast Cancer Immunotherapy: Facts and Hopes. Clin Cancer Res. 2018 Feb 1;24(3):511-520. doi: 10. 1158/1078-0432. CCR-16-3001. Epub 2017 Aug 11. PMID: 28801472; PMCID: PMC5796849.

[6] Wang Qin. Changes of immune cells and their curative effects of radiotherapy combined or non-com-joined immunotherapy for different tumors [D]. Southern Medical University, 2022. DOI:10. 27003/d. cnki. gojyu. 2022. 000321.

[7] Dovedi SJ, Lipowska-Bhalla GL, Beers SA，et al． Anti-tumor efficacy of radiation and immunotherapy combinations is dependent on dendritic cell activation of effector CD8 + T-cells [J]. Cancer Immunol Res, 2016, 4(7) : 621-630.

[8] Zhang B, Bowerman NA, Salama JK, et al. Induced sensitization of tumor stroma leads to eradication of established cancer by T cells [J]. J Exp Med, 2007, 204(1) :49-55.

[9] Liu Chao, Wu Shikai. Research progress on the anti-tumor immune mechanism of radiotherapy combined immunotherapy [J]. Military Medicine, 2016, 40 (04): 353-355+359.

[10] Burnette B, Weichselbaum RR. The immunology of ablative radiation [J]. Semin Radiat Oncol, 2015, 25(1) : 40-45.

[11] Persa E, Balogh A, Safrany G, et al. The effect of ionizing radiation on regulatory T cells in health and disease [J] . Cancer Lett, 2015, 368(2):252-261.

[12] Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice [J]. J Clin Invest, 2014, 124(2):687-695.

[13] Chang CH, Qiu J, O'Sullivan D, Buck MD, Noguchi T, Curtis JD, Chen Q, Gindin M, Gubin MM, van der Windt GJ, Tonc E, Schreiber RD, Pearce EJ, Pearce EL. Metabolic Competition in the Tumor Microenvironment Is a Driver of Cancer Progression. Cell. 2015 Sep 10;162(6):1229-41. doi: 10. 1016/j. cell. 2015. 08. 016. Epub 2015 Aug 27. PMID: 26321679; PMCID: PMC4864363.

[14] Mediratta K, El-Sahli S, D'Costa V, et al. Current progresses and challenges of immunotherapy in triple-negative breast cancer [J]. Cancers (Basel), 2020, 12(12):E3529.

[15] Li Chenyang, Liu Qiufang, Wang Tianchang, etc. Research progress on advanced breast cancer radiotherapy combined with PD-1/PD-L1 inhibitor treatment [J]. Chinese Journal of Tumor Prevention and Control, 2023, 30(07):436-442. DOI:10. 16073/j. cnki. cjcpt. 2023. 07. 10.

[16] Ho AY, Barker CA, Arnold BB, Powell SN, Hu ZI, Gucalp A, Lebron-Zapata L, Wen HY, Kallman C, D'Agnolo A, Zhang Z, Flynn J, Dunn SA, McArthur HL. A phase 2 clinical trial assessing the efficacy and safety of pembrolizumab and radiotherapy in patients with metastatic triple-negative breast cancer. Cancer. 2020 Feb 15;126(4):850-860. doi: 10. 1002/cncr. 32599. Epub 2019 Nov 20. PMID: 31747077.

[17] Niesel K, Schulz M, Anthes J, Alekseeva T, Macas J, Salamero-Boix A, Möckl A, Oberwahrenbrock T, Lolies M, Stein S, Plate KH, Reiss Y, Rödel F, Sevenich L. The immune suppressive microenvironment affects efficacy of radio-immunotherapy in brain metastasis. EMBO Mol Med. 2021 May 7;13(5):e13412. doi: 10. 15252/emmm. 202013412. Epub 2021 Mar 23. PMID: 33755340; PMCID: PMC8103101.

[18] Kim H, Chung JH. PD-L1 Testing in Non-small Cell Lung Cancer: Past, Present, and Future [J]. J Pathol Transl Med. 2019, 53(4): 199-206. doi: 10. 4132/jptm. 2019. 04. 24.

[19] Omori S, Kenmotsu H, Abe M, et al. Changes in programmed death ligand 1 expression in non-small cell lung cancer patients who received anticancer treatments [J]. Int J Clin Oncol. 2018, 23(6): 1052-1059. doi: 10. 1007/s10147-018-1305-4

[20] Ilie M, Long-Mira E, Bence C, et al. Comparative study of the PD-L1 status between surgically resected specimens and matched biopsies of NSCLC patients reveal major discordances: a potential issue for anti-PD-L1 therapeutic strategies [J]. Ann Oncol. 2016, 27(1): 147-153. doi: 10. 1093/annonc/mdv489.

[21] Kim S, Koh J, Kwon D, et al. Comparative analysis of PD-L1 expression between primary and metastatic pulmonary adenocarcinomas [J]. Eur J Cancer. 2017, 75: 141-149. doi: 10. 1016/ j. ejca. 2017. 01. 004.

[22] Herbst RS, Baas P, Perez-Gracia JL, et al. Use of archival versus newly collected tumor samples for assessing PD-L1 expression and overall survival: an updated analysis of KEYNOTE-010 trial [J]. Ann Oncol. 2019, 30(2): 281-289. doi: 10. 1093/annonc/mdy545.
[23] Chen J, Jiang CC, Jin L, Zhang XD. Regulation of PD-L1: a novel role of pro-survival signalling in cancer [J]. Ann Oncol. 2016, 27(3): 409-416. doi: 10. 1093/annonc/mdv615.