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Sex Disparities in Cancer Immunotherapy: A Review

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ABSTRACT

Cancer immunotherapy has revolutionized cancer treatment, particularly through immune checkpoint inhibitors (ICIs) targeting proteins like PD-1, PD-L1, and CTLA-4. While these therapies have shown significant survival benefits across various cancers, sex-based disparities in treatment response and outcomes have emerged. This review explores the mechanisms behind these differences, focusing on genetic, hormonal, and immune system variations between male and female patients. Women tend to exhibit stronger immune responses due to the presence of two X chromosomes and the immunostimulatory effects of estrogen, which enhances immune activity. Conversely, men's single X chromosome and the immunosuppressive effects of testosterone contribute to a less vigorous immune response. These biological differences manifest in clinical outcomes, with men generally experiencing better overall survival rates from ICIs, while women are more prone to immune-related adverse events (irAEs), including autoimmune toxicities. However, in certain cases, women may demonstrate more robust long-term survival benefits from treatments such as CTLA-4 inhibitors, despite higher toxicity risks. Beyond ICIs, sex disparities also extend to adoptive cell therapies (ACT) and cancer vaccines, where female patients often display stronger immune responses but face increased risks of side effects, necessitating personalized approaches to therapy. The review also discusses emerging research on the tumor microenvironment (TME), gut microbiome, and sex-specific pharmacokinetics and pharmacodynamics as contributing factors to these disparities. Understanding these mechanisms is critical for improving cancer immunotherapy outcomes for both sexes. Future research should focus on investigating the role of sex hormones, the microbiome, and developing biomarkers to better predict responses to immunotherapy. Clinically, the findings highlight the need for tailored treatment strategies that account for sex-specific differences, aiming for more equitable and effective cancer care.

Keywords: Cancer immunotherapy, Immune checkpoint inhibitors (ICIs), Sex-based disparities, PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors

INTRODUCTION

Cancer immunotherapy has emerged as a groundbreaking approach to treating various types of cancer, with immune checkpoint inhibitors (ICIs) being one of the most significant advancements in recent years [1]. ICIs, which target proteins like PD-1, PD-L1, and CTLA-4, work by releasing the brakes on the immune system, allowing it to recognize and attack cancer cells more effectively [2]. These therapies have revolutionized the treatment landscape for cancers such as melanoma, non-small cell lung cancer, and renal cell carcinoma, where they have demonstrated substantial improvements in survival rates and disease management [3]. However, the effectiveness of immunotherapy is not uniform across all patient populations. One important factor contributing to this variability is the patient's sex [4]. Studies have shown that male and female patients exhibit different response rates, experience varying side effect profiles, and have distinct survival outcomes when undergoing cancer immunotherapy [5]. This sex-based disparity is likely influenced by a complex interplay of biological, genetic, hormonal, and immune factors. For instance, differences in immune system regulation, hormonal levels, and genetic expression between men and women may influence how their bodies respond to ICIs [6]. Understanding these sex-specific differences is vital for several reasons. First, it could help clinicians tailor treatment plans more effectively, improving outcomes for both men and women. Second, it could lead to the development of more

personalized immunotherapy strategies, where treatment is adjusted based on individual patient characteristics, including sex [7]. Lastly, it could help reduce disparities in cancer care, ensuring that both male and female patients receive the most effective and least harmful treatment [8]. This review aims to explore the mechanisms behind sex-specific differences in cancer immunotherapy responses and to highlight the clinical implications of these findings. By delving into the biological and immunological factors that contribute to these disparities, we hope to provide insights that can enhance treatment regimens and lead to more equitable and effective cancer care for all patients [9].

Biological and Immunological Differences between Sexes

Genetic and Molecular Factors: At the genetic level, men and women differ significantly due to their chromosomal makeup—females possess two X chromosomes, while males have one X and one Y chromosome [10]. This chromosomal distinction has a direct impact on immune function, as the X chromosome contains a high concentration of immune-related genes, including those involved in regulating the immune system's response to cancer [11]. For females, the presence of two X chromosomes provides genetic redundancy, meaning that even if there are mutations or dysfunctions in one of the X-linked genes, the other chromosome can compensate, leading to potentially more stable and robust immune responses [12].

Males, on the other hand, have only one X chromosome, making them more vulnerable to the effects of mutations or deletions in X-linked immune-regulatory genes. This lack of genetic redundancy could explain why men are more prone to certain infections and exhibit weaker immune responses in some scenarios, which may extend to cancer immunotherapy. Additionally, the Y chromosome has a more limited set of genes related to immune regulation, further contributing to the observed disparities in immune function between the sexes [13].

Hormonal Influence: Sex hormones play a critical role in shaping immune function, with estrogen and testosterone exerting opposing effects on immune responses. Estrogen, the primary female sex hormone, enhances immune activity by promoting the function and activation of various immune cells, including T cells, macrophages, and dendritic cells. This hormone enhances antigen presentation, boosts the proliferation of cytotoxic T cells, and encourages a more vigorous immune response, potentially improving the efficacy of immunotherapies in women [14].

Conversely, testosterone, the predominant male hormone, has an immunosuppressive effect. It dampens the immune response by reducing the activity of immune cells, leading to decreased inflammation and immune surveillance. This immunosuppressive role of testosterone may partially explain why men tend to have weaker responses to cancer immunotherapy. These hormonal differences highlight how sex-based variations in hormone levels can influence immune function and may contribute to differential responses to immunotherapies in cancer patients [15].

Immune System Differences: In general, women exhibit a more active and robust immune system compared to men. This is reflected in their stronger responses to infections and vaccines, as well as their higher production of pro-inflammatory cytokines [16]. The heightened immune activity in women may be advantageous in mounting anti-tumor responses during cancer immunotherapy, leading to more effective tumor elimination. However, this heightened immune response also comes with risks. Women are more susceptible to developing autoimmune diseases, conditions where the immune system mistakenly attacks the body's own tissues [17]. This overactive immune response could also contribute to women experiencing more severe immune-related adverse events (irAEs) during cancer immunotherapy, such as inflammation of healthy organs. The increased likelihood of irAEs in women may be a double-edged sword, providing stronger anti-tumor activity while also increasing the risk of potentially harmful side effects [18]. Together, these biological and immunological differences between the sexes help to explain the variability in cancer immunotherapy outcomes. Women may experience stronger immune responses and better anti-tumor effects, but they also face a higher risk of severe side effects. On the other hand, men may have weaker immune responses but a lower likelihood of irAEs. Understanding these differences is crucial for developing personalized immunotherapy strategies that account for sex-based variations, ultimately improving treatment outcomes for both men and women [19].

Clinical Evidence of Sex Disparities in Immunotherapy

Sex-based disparities in cancer immunotherapy have become evident through numerous clinical studies and trials, particularly regarding immune checkpoint inhibitors (ICIs), adoptive cell therapies, and cancer vaccines. These differences have significant implications for the efficacy, toxicity, and overall survival outcomes for male and female patients [20].

Immune Checkpoint Inhibitors (ICIs): ICIs have been a major breakthrough in cancer treatment, with drugs targeting the PD-1/PD-L1 and CTLA-4 pathways playing critical roles in enhancing the immune system's ability to recognize and destroy cancer cells. However, the efficacy of these treatments is not the same for all patients, and sex-based differences have been reported in several studies [21].

- **PD-1/PD-L1 Inhibitors**: These inhibitors, such as pembrolizumab and nivolumab, block the PD-1/PD-L1 pathway, which tumors use to evade immune detection. Clinical trials in cancers such as non-small cell lung cancer (NSCLC) and melanoma have shown that male patients often experience better overall survival benefits compared to female patients. For example, in NSCLC, some studies suggest that men treated with PD-1/PD-L1 inhibitors have a more prolonged survival than women.

However, while men may exhibit better survival outcomes, female patients tend to experience higher rates of immune-related adverse events (irAEs), particularly autoimmune toxicities. Women are more prone to developing severe side effects such as colitis, pneumonitis, and dermatitis, which can sometimes necessitate discontinuation of therapy [22]. This suggests that while women may experience more potent immune responses to these drugs, the intensity of their immune system activation also puts them at greater risk for harmful side effects.

- **CTLA-4 Inhibitors**: CTLA-4 inhibitors, such as ipilimumab, work by blocking CTLA-4, a protein that downregulates the immune response. Studies have shown that female patients treated with CTLA-4 inhibitors often experience more significant toxicities compared to their male counterparts. These toxicities can include severe inflammatory responses and autoimmune disorders.

Despite the higher toxicity, female patients may also enjoy better long-term survival benefits from CTLA-4 inhibitors. For example, women with metastatic melanoma treated with ipilimumab have demonstrated improved long-term survival rates compared to men. This suggests that although women may experience more frequent or severe side effects, their immune systems might mount a more durable and effective anti-tumor response [23].

Adoptive Cell Therapy and Cancer Vaccines

Sex disparities are not limited to ICIs but also extend to other forms of immunotherapy, such as adoptive cell therapies and cancer vaccines. These therapies harness the patient's own immune cells to target and eliminate cancer cells more effectively.

- **Adoptive Cell Therapy (ACT)**: In ACT, T cells are extracted from a patient, engineered to enhance their cancer-fighting abilities, and then reinfused into the body. Clinical data indicate that women generally exhibit stronger responses to ACT than men [24]. This is likely due to women's more robust T-cell activity, which is influenced by genetic, hormonal, and immune system differences. For example, female patients may generate a higher number of active T cells that can better recognize and attack tumor cells.

On the other hand, male patients often require higher doses of T cells or combination therapies to achieve comparable results. These combination therapies may include the use of cytokines or other immune-stimulating agents to enhance the T-cell response in men [25]. These differences highlight the need for sex-specific considerations in the administration and dosing of adoptive cell therapies.

- **Cancer Vaccines**: Cancer vaccines, which aim to stimulate the immune system to recognize and attack cancer cells, have also shown sex-based differences in efficacy. Female patients tend to generate more potent immune responses to cancer vaccines, likely due to their higher baseline immune activity. This heightened response can lead to better clinical outcomes in some cases, but it may also increase the risk of vaccine-related side effects.

In contrast, male patients often have weaker responses to cancer vaccines and may require additional immunostimulatory interventions or combination therapies to achieve optimal efficacy [12]. These sex-based differences in response rates further underscore the importance of personalizing immunotherapy based on patient characteristics, including sex.

Implications for Clinical Practice

The growing body of evidence highlighting sex disparities in cancer immunotherapy has significant implications for clinical practice. Understanding these differences can help physicians tailor treatment regimens more effectively, potentially improving survival outcomes for both men and women [9]. For instance, clinicians might consider closer monitoring of irAEs in female patients and the use of combination therapies or higher dosing strategies for male patients. Personalized approaches to immunotherapy that account for sex-based biological and immunological differences will be critical in optimizing treatment efficacy and minimizing toxicities for all patients.

Potential Mechanisms for Sex Disparities in Immunotherapy

Tumor Microenvironment (TME): The tumor microenvironment plays a crucial role in determining the efficacy of immunotherapy. Sex differences in the TME, such as variations in immune cell infiltration, cytokine profiles, and the expression of immune checkpoints, can influence how male and female patients respond to treatment [10]. For instance, male patients may exhibit higher expression of immunosuppressive factors within the TME, reducing the effectiveness of ICIs.

Microbiome Influence: Emerging research suggests that the gut microbiome plays a role in shaping the response to immunotherapy. Differences in the gut microbiota between men and women may contribute to variations in immune responses and treatment outcomes [9]. Certain bacterial strains have been linked to enhanced responses to ICIs, and these strains may be more prevalent in one sex than the other.

Pharmacokinetics and Pharmacodynamics: Sex-based differences in drug metabolism and distribution also affect immunotherapy outcomes. Women generally have a higher body fat percentage and different drug clearance rates than men, which can alter the pharmacokinetics of immunotherapeutic agents [17]. These variations may require sex-specific dosing strategies to optimize treatment efficacy.

Future Directions and Research Gaps

While significant progress has been made in understanding sex disparities in cancer immunotherapy, several research gaps remain. Future studies should focus on:

- Investigating the role of sex hormones in modulating immune responses to cancer.
- Exploring the impact of the microbiome on sex-specific immunotherapy outcomes.
- Conducting long-term studies to assess survival differences between men and women receiving various forms of immunotherapy.
- Developing predictive biomarkers that can identify which patients are most likely to benefit from immunotherapy based on sex-specific factors.

CONCLUSION

The review highlights the significant sex disparities in cancer immunotherapy, emphasizing the complex interplay of biological, hormonal, and immune factors that contribute to differences in treatment outcomes between men and women. Immune checkpoint inhibitors (ICIs), adoptive cell therapies, and cancer vaccines demonstrate varying efficacy, toxicity, and survival rates depending on the patient's sex. Men often experience better overall survival benefits from ICIs, while women may exhibit stronger immune responses but are at greater risk for immune-related adverse events (irAEs). These differences are further influenced by genetic factors, hormonal variations, and immune system activity, with women displaying more robust immune functions that can lead to both enhanced anti-tumor activity and increased side effects.

Clinically, these findings underscore the need for personalized approaches to immunotherapy that consider sex-based differences to optimize treatment efficacy and minimize toxicity. Future research should focus on understanding the underlying mechanisms driving these disparities, such as the role of sex hormones, the tumor microenvironment, and the microbiome. Additionally, long-term studies are required to develop sex-specific treatment protocols, ensuring that both male and female patients receive the most effective and least harmful cancer therapies. By addressing these gaps, clinicians can move toward more equitable and tailored cancer care for all patients.

REFERENCES

1. Conforti, F., Pala, L., & Bagnardi, V. (2022). Sex-based disparities in immune checkpoint inhibitor therapy: A systematic review and meta-analysis. JAMA Oncology, 8(2), 272-278. https://doi.org/10.1001/jamaoncol.2021.6738
2. Obeagu, E. I., Alum, E. U., Obeagu, G.U. and Ugwu, O. P. C. Prostate Cancer: Review on Risk Factors. Eurasian Experiment Journal of Public Health (EEJPH). 2023; 4(1): 4-7.https://www.eejournals.org/public/uploads/1688032824_872978821ba373725554.pdf
3. Ibiam, U. A., Uti, D. E., Ejeogo, C. C., Orji, O. U., Aja, P. M., Ezeaani, N. N., Alum, E. U.,Chukwu, C., AlokeC., Chinedum, K. E., Agu, P. and Nwobodo, V.In Vivo and in Silico Assessment of Ameliorative Effects of Xylopiaaethiopica on Testosterone Propionate-Induced Benign Prostatic Hyperplasia. Pharmaceut Fronts. 2023;5: e64–e76.DOI:10.1055/s-0043-1768477
4. Alum, E. U., Inya, J. E., Ugwu, O. P. C., Obeagu, I. E., Aloke, C., Aja, P. M., Okpata, M. G., John, E. C., Orji, M. O. and Onyema, O. Ethanolic leaf extract of Daturastramonium attenuates Methotrexate-induced Biochemical Alterations in Wistar Albino rats. RPSPharmacy and Pharmacology Reports, 2023; 2(1):1–6. doi: 10.1093/rpsppr/rqac011.
5. Aja, P. M., Agu, P. C., Ezeh, E. M., Awoke, J. N., Ogwoni, H. A., Deusdedit, T., Ekpono, E. U., Igwenyi, I. O., Alum, E. U.,Ugwuja, E. I., Ibiam, U. A., Afiukwa, C. A. and Adegboyega, A. E. Prospect into therapeutic potentials of Moringa oleifera phytocompounds against cancer upsurge: de novo synthesis of test compounds, molecular docking, and ADMET studies. Bulletin of the National Research Centre. 2021; 45(1): 1-18. https://doi.org/10.1186/s42269-021-00554-6.

6. Obeagu, E. I., Ahmed, Y. A., Obeagu, G. U., Bunu, U. O., Ugwu, O. P. C. and Alum, E. U. Biomarkers of breast cancer: Overview. Int. J. Curr. Res. Biol. Med., 2023; (1): 8-16. DOI:10.22192/ijcrbm.2023.08.01.002.
7. Klein, S. L., & Flanagan, K. L. (2022). Sex differences in immune responses. Nature Reviews Immunology, 22(10), 626-639. https://doi.org/10.1038/s41577-022-00696-2
8. Wu, Y., Guo, W., & Xie, J. (2023). Sex differences in immune checkpoint inhibitors for advanced cancers: A meta-analysis of randomized clinical trials. European Journal of Cancer, 187, 165-174. https://doi.org/10.1016/j.ejca.2023.01.006
9. Pinato, D. J., Wilkinson, S. M., & Sharma, R. (2021). Sex and gender differences in cancer immunotherapy efficacy: a systematic review and meta-analysis. Cancer Immunology, Immunotherapy, 70(8), 2211-2222. https://doi.org/10.1007/s00262-021-02881-6
10. Alum, E. U., Ugwu, O. P. C., Obeagu, E. I.,Ugwu, C. N. Beyond Conventional Therapies: Exploring Nutritional Interventions for Cervical Cancer Patients, J, Cancer Research and Cellular Therapeutics, 8(1);1-6. DOI:10.31579/2640-1053/180
11. Ibiam U. A., Uti, D. E., Ejeogo, C.C., Orji, O. U. Aja, P. M., Ezeani, N. N., Alum, E. U., Chukwu, C., Aloke, C., Itodo, M. O., Agada, S. A., Umoru, G. U., Obeten, U. N., Nwobodo, V. O. G., Nwadum, S. K., Udoudoh, M. P. Xylopiaaethiopica Attenuates Oxidative Stress and Hepatorenal Damage in Testosterone Propionate-Induced Benign Prostatic Hyperplasia in Rats. Journal of Health and Allied Sciences. 2024, 01: 1-148. https://doi.org/10.1055/s-0043-1777836.
12. Lee, C. K., Man, J., & Lord, S. (2022). Sex differences in immune checkpoint inhibitors' efficacy across cancer types: A systematic review and meta-analysis. Journal for Immuno Therapy of Cancer, 10(3), e004664. https://doi.org/10.1136/jitc-2022-004664
13. Alum, E, U, Obeagu E, I, Ugwu O, P, C. Cervical Cancer Unveiled: Insights into HPV, Risks, and Therapeutic Frontiers. Elite Journal of Public Health, 2024; 2 (6): 55-66.
14. Ugwu O, P, C, Anyanwu C, N, Alum E, U, Okon M, B, Egba S, I, Uti D, E and Awafung E, A. (2024).CRISPR-Cas9 Mediated Gene Editing for Targeted Cancer Therapy: Mechanisms, Challenges, and Clinical Applications. Newport International Journal of Biological and AppliedSciences,5(1):97-102. https://doi.org/10.59298/NIJBAS/2024/5.1.9297102
15. Alum E, U., Uti D, E., Obeagu E, I., Ugwu O, P, C., Alum B, N.. Cancer's Psychosocial Aspects: Impact on Patient Outcomes. Elite Journal of Medicine, 2024; 2(6): 32-42.
16. Ferrara, R., Mezquita, L., & Auclin, E. (2021). Sex-based differences in immune checkpoint inhibitors across multiple cancers: A meta-analysis of randomized clinical trials. The Lancet Oncology, 22(3), 348-359. https://doi.org/10.1016/S1470-2045(21)00035-6
17. Obeagu, E. I., Omar, D. E., Bunu, U. O., Obeagu, G. U., Alum, E. U. and Ugwu, O. P. C. Leukaemia burden in Africa. Int. J. Curr. Res. Biol. Med., 2023; (1): 17- 22. DOI:10.22192/ijcrbm.2023.08.01.003
18. Alum, E. U., Famurewa, A. C., Orji, O. U., Aja, P. M., Nwite, F., Ohuche, S. E., Ukasoanya, S. C., Nnaji, L. O., Joshua, D., Igwe, K. U. and Chima, S. F. Nephroprotective effects of Daturastramonium leaves against methotrexate nephrotoxicity via attenuation of oxidative stress-mediated inflammation and apoptosis in rats. Avicenna Journal of Phytomedicine. 2023; 13(4): 377-387. doi: 10.22038/ ajp.2023.21903.
19. Amadori, A., Arigoni, M., & Baldessari, C. (2021). Sex-related differences in anti-tumor immune response and toxicity with immune checkpoint inhibitors. Clinical Cancer Research, 27(9), 2549-2560. https://doi.org/10.1158/1078-0432.CCR-20-4139
20. Alum, E. U., Obeagu, E. I., Ugwu, O. P. C., Orji, O. U., Adepoju, A. O., Amusa, M. O. Edwin, N. Exploring natural plant products in breast cancer management: A comprehensive review and future prospects. International Journal of Innovative and Applied Research. 2023; 11(12):1-9.Article DOI:10.58538/IJIAR/2055. DOI URL:http://dx.doi.org/10.58538/IJIAR/2055
21. Márquez-Ruiz, D., Valencia-Mercado, M., & Romero-Bueno, F. (2023). Sex disparities in cancer immunotherapy: Biological mechanisms and clinical implications. Cancer Letters, 565, 215785. https://doi.org/10.1016/j.canlet.2023.215785
22. Falchook, G. S., Stevoff, C., & Feng, X. (2022). Sex-based differences in safety and efficacy of immune checkpoint inhibitors across multiple cancer types: A real-world analysis. Oncologist, 27(6), 435-444. https://doi.org/10.1093/oncolo/oyab010
23. Alum, E. U., Ugwu, O. P. C., Obeagu, E. I. Cervical Cancer Prevention Paradox: Unveiling Screening Barriers and Solutions, J, Cancer Research and Cellular Therapeutics. 2024, 8(2):1-5. DOI:10.31579/2640-1053/182

24. Alum, E, U., Uti D, E., Obeagu E, I., Ugwu, O, P, C., Alum, B, N. Cancer's Psychosocial Aspects: Impact on Patient Outcomes. Elite Journal of Medicine, 2024; 2(6): 32-42.
25. Gupta, S., Kurian, A. W., & Saha, P. (2023). Sex and gender considerations in the use of immune checkpoint inhibitors: Implications for practice and research. JCO Oncology Practice, 19(7), e1104-e1112. https://doi.org/10.1200/OP.22.00702

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