Evaluation of the Effectiveness of Immunotherapy in Combination with Conventional Treatment Modalities in Early-Stage Breast Cancer

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ABSTRACT

Breast cancer remains the most frequently diagnosed malignant disease among women worldwide and continues to represent a major cause of cancer-related morbidity and mortality. Despite significant advances in screening, early detection, and multidisciplinary treatment, breast cancer poses ongoing clinical challenges due to its biological heterogeneity and variable response to therapy. Early-stage breast cancer, generally defined as stages I–II according to the TNM classification, is associated with favorable survival outcomes; however, a proportion of patients still experience disease recurrence, progression, or treatment-related toxicity

Keywords:

Introduction

Breast cancer remains the most frequently diagnosed malignant disease among women worldwide and continues to represent a major cause of cancer-related morbidity and mortality. Despite significant advances in screening, early detection, and multidisciplinary treatment, breast cancer poses ongoing clinical challenges due to its biological heterogeneity and variable response to therapy. Early-stage breast cancer, generally defined as stages I–II according to the TNM classification, is associated with favorable survival outcomes; however, a proportion of patients still experience disease recurrence, progression, or treatment-related toxicity. These limitations highlight the need for innovative therapeutic strategies capable of improving long-term outcomes while minimizing unnecessary treatment burden[1,5,7].

Traditionally, the management of early-stage breast cancer has relied on a combination of surgery, chemotherapy, radiotherapy, endocrine therapy, and targeted agents depending on tumor subtype and risk profile. Chemotherapy and radiotherapy remain cornerstone modalities, particularly for patients with high-risk disease features, such as aggressive tumor biology or lymph node involvement. While these approaches have significantly reduced recurrence rates and improved survival, they are associated with substantial acute and long-term toxicities, including cardiotoxicity, neurotoxicity, secondary malignancies, and impaired quality of life. Moreover, conventional treatments are not equally effective across all molecular subtypes, underscoring the need for more precise and biologically driven therapeutic interventions[2,5].

In recent years, immunotherapy has emerged as a transformative approach in oncology, demonstrating remarkable clinical efficacy in several solid tumors, including melanoma, lung cancer, and renal cell carcinoma. Immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) have shown the ability to restore antitumor immune responses

and achieve durable clinical benefits. These successes have stimulated intense interest in exploring the role of immunotherapy in breast cancer, a disease historically considered to be less immunogenic than other malignancies.

Accumulating evidence suggests that the immune system plays a critical role in breast cancer development, progression, and response to therapy. The presence of tumor-infiltrating lymphocytes, expression of immune checkpoint molecules, and features of the tumor immune microenvironment have been associated with prognosis, particularly in biologically aggressive subtypes such as triple-negative and HER2-positive breast cancer. Early-stage breast cancer represents a particularly attractive setting for immunotherapeutic intervention, as tumor burden is lower, immune function is less compromised, and the likelihood of eradicating micrometastatic disease is higher[5,8].

The biological rationale for combining immunotherapy with conventional treatment modalities is supported by growing preclinical and clinical evidence. Chemotherapy, beyond its direct cytotoxic effects, can modulate the immune microenvironment by inducing immunogenic cell death, enhancing tumor antigen release, and reducing immunosuppressive cell populations such as regulatory T cells and myeloid-derived suppressor cells. Similarly, radiotherapy has been shown to increase tumor immunogenicity through enhanced antigen presentation, upregulation of major histocompatibility complex molecules, and activation of innate and adaptive immune responses. These immunomodulatory effects create a synergistic framework in which traditional therapies may potentiate the efficacy of immunotherapy.

In the context of early-stage breast cancer, combination strategies involving immunotherapy and chemotherapy or radiotherapy are being actively investigated, particularly in the neoadjuvant and adjuvant settings. Neoadjuvant therapy provides a unique opportunity to assess treatment response through pathological complete response, a surrogate marker associated with improved survival outcomes. The addition of immunotherapy to neoadjuvant chemotherapy has demonstrated promising improvements in pathological response rates, especially in triple-negative breast cancer, suggesting enhanced antitumor immune activation. Adjuvant immunotherapy, on the other hand, aims to eliminate minimal residual disease following surgery and reduce the risk of recurrence[6,8].

Despite these advances, the integration of immunotherapy into early-stage breast cancer treatment remains complex and requires careful evaluation. Not all patients derive equal benefit from immune-based approaches, and the identification of reliable predictive biomarkers remains an unmet need. PD-L1 expression, tumor-infiltrating lymphocytes, and genomic immune signatures have shown potential as biomarkers; however, their predictive value is not absolute, and responses have been observed even in biomarker-negative tumors. This variability underscores the importance of comprehensive evaluation of immunotherapy effectiveness in combination with established treatment modalities.

Safety considerations are particularly relevant in early-stage disease, where the intent of treatment is curative. Immune-related adverse events, while generally manageable, may involve multiple organ systems and require prompt recognition and intervention. When immunotherapy is combined with chemotherapy or radiotherapy, the potential for overlapping toxicities necessitates careful monitoring and optimization of treatment protocols. Balancing therapeutic efficacy with safety and quality of life is therefore a central concern in the early-stage setting[3,7,8].

Another important consideration is the long-term impact of immunotherapy on disease outcomes. While improvements in pathological response rates are encouraging, mature data on disease-free and overall survival are still emerging. Long-term follow-up is essential to determine whether early immunotherapeutic intervention translates into sustained survival benefits and reduced recurrence rates. Furthermore, cost-effectiveness and accessibility of immunotherapy remain significant challenges, particularly in healthcare systems with limited resources.

In this context, a comprehensive evaluation of the effectiveness of immunotherapy combined with conventional treatment modalities in early-stage breast cancer is highly relevant. Understanding the biological rationale, clinical efficacy, safety profile, and limitations of such combination strategies is essential for optimizing patient selection and treatment design. This article aims to review current evidence regarding the use of immunotherapy in combination with chemotherapy and radiotherapy in early-stage breast cancer, assess its clinical benefits and challenges, and discuss future directions in this rapidly evolving field.

Biological Rationale for Immunotherapy in Breast Cancer

Breast cancer was historically considered a weakly immunogenic tumor. However, growing evidence suggests that the tumor immune microenvironment plays a crucial role in disease progression and response to therapy. Tumor-infiltrating lymphocytes (TILs), immune checkpoint expression, and cytokine signaling pathways have been shown to influence prognosis, especially in biologically aggressive subtypes such as triple-negative breast cancer (TNBC) and HER2-positive disease[2,8].

Immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) and its ligand PD-L1 enhance antitumor immune responses by restoring T-cell activity. Chemotherapy and radiotherapy can further modulate tumor immunogenicity by inducing immunogenic cell death, increasing antigen presentation, and promoting immune cell infiltration. These effects provide a strong biological rationale for combining immunotherapy with traditional treatment modalities in early-stage breast cancer.

Immunotherapy in Early-Stage Breast Cancer

The majority of immunotherapy studies in breast cancer have focused on advanced or metastatic disease. However, recent clinical trials have shifted attention toward early-stage settings, where immune-based strategies may improve pathological response rates and reduce long-term recurrence risk.

In early-stage breast cancer, immunotherapy is primarily investigated in the neoadjuvant and adjuvant settings. Neoadjuvant immunotherapy offers the advantage of early immune activation in the presence of intact tumor antigens and allows assessment of treatment response through pathological complete response (pCR). Adjuvant immunotherapy aims to eradicate minimal residual disease and prevent relapse following definitive local treatment[1,8].

Combination of Immunotherapy and Chemotherapy

Chemotherapy remains a cornerstone of early-stage breast cancer treatment, particularly in high-risk disease. Beyond its cytotoxic effects, chemotherapy can enhance immune responses by reducing immunosuppressive cells within the tumor microenvironment and increasing tumor antigen release.

Clinical trials evaluating the combination of immune checkpoint inhibitors with chemotherapy in early-stage breast cancer have demonstrated encouraging results, particularly in TNBC. Several studies have shown significantly higher pCR rates in patients receiving combined chemo-immunotherapy compared with chemotherapy alone. Achieving pCR is associated with improved event-free survival and overall survival, highlighting the clinical relevance of these findings.

Importantly, the benefit of immunotherapy appears to be more pronounced in tumors with higher immune infiltration and PD-L1 expression, although responses have also been observed in PD-L1–negative cases. These findings suggest that chemotherapy may sensitize tumors to immunotherapy, broadening its potential applicability[7,8,9].

Combination of Immunotherapy and Radiotherapy

Radiotherapy is an integral component of breast-conserving treatment and plays a key role in local disease control. In addition to its local effects, radiotherapy can induce systemic immune responses through the so-called abscopal effect, whereby irradiation of a tumor site leads to regression of distant, non-irradiated lesions.

Preclinical and early clinical studies indicate that radiotherapy may synergize with

immunotherapy by increasing tumor antigen presentation, enhancing T-cell infiltration, and upregulating immune checkpoint molecules. In early-stage breast cancer, the combination of radiotherapy and immunotherapy is being explored as a strategy to improve local control and systemic antitumor immunity. Although clinical data are still limited, preliminary results suggest acceptable safety profiles and potential enhancement of immune-mediated tumor control[1,8].

Clinical Outcomes and Efficacy

The primary efficacy endpoints used to evaluate immunotherapy in early-stage breast cancer include pathological complete response, event-free survival, disease-free survival, and overall survival. Current evidence indicates that the addition of immunotherapy to standard chemotherapy significantly increases pCR rates, particularly in TNBC. Early survival data suggest a reduction in recurrence risk, although long-term follow-up is still ongoing.

In hormone receptor-positive early-stage breast cancer, the benefit of immunotherapy appears to be more modest, likely due to lower tumor immunogenicity. Ongoing trials aim to identify biomarkers that can predict which patients are most likely to benefit from immune-based approaches.

Safety and Toxicity Considerations

The combination of immunotherapy with chemotherapy or radiotherapy raises concerns regarding additive toxicity. Immune-related adverse events, including dermatologic, gastrointestinal, endocrine, and pulmonary complications, have been reported. However, in early-stage settings, most immune-related toxicities are manageable with appropriate monitoring and timely intervention.

Importantly, the overall safety profile of combined treatment regimens has been considered acceptable in clinical trials, with no significant compromise in treatment delivery. Long-term safety data remain essential, particularly given the curative intent of early-stage breast cancer therapy[2,7].

Challenges and Limitations

Despite the growing interest in immunotherapy for early-stage breast cancer and the encouraging results reported in recent clinical trials, several challenges and limitations currently restrict its widespread adoption in routine clinical practice. These challenges relate to biological heterogeneity, patient selection, toxicity, methodological issues in clinical trials, and broader socioeconomic considerations.

One of the principal challenges is the intrinsic heterogeneity of breast cancer. Unlike tumors such as melanoma or non–small cell lung cancer, breast cancer exhibits considerable variability in immune responsiveness across molecular subtypes. While triple-negative and, to a lesser extent, HER2-positive breast cancers tend to demonstrate higher levels of tumor-infiltrating lymphocytes and immune checkpoint expression, hormone receptor–positive tumors are generally less immunogenic. As a result, the clinical benefit of immunotherapy is unevenly distributed, and many patients with early-stage disease may derive limited or no advantage from immune-based treatments. This heterogeneity complicates treatment decision-making and underscores the need for more precise predictive tools[2,11].

Another major limitation is the lack of robust and universally accepted biomarkers to guide patient selection. Although PD-L1 expression, tumor-infiltrating lymphocyte density, and immune gene signatures have been explored as potential predictors of response, none have demonstrated sufficient sensitivity or specificity to serve as definitive selection criteria. Furthermore, responses to immunotherapy have been observed in some patients lacking these markers, while others with positive biomarkers fail to benefit. This uncertainty increases the risk of overtreatment and exposes patients to unnecessary toxicity and costs.

Toxicity and safety concerns represent a particularly important challenge in early-stage breast cancer, where the primary treatment goal is cure. Immune-related adverse events, including dermatologic, gastrointestinal, endocrine, pulmonary, and hepatic toxicities, may occur even after limited exposure to immune checkpoint inhibitors. Although most adverse events are manageable, some may be severe or irreversible, such as autoimmune endocrinopathies. When immunotherapy is

combined with chemotherapy or radiotherapy, the potential for additive or overlapping toxicities further complicates treatment planning. Long-term safety data in the early-stage setting remain limited, and the full impact of immune-related toxicities on survivorship and quality of life is not yet fully understood[2,8].

Methodological limitations of current clinical trials also pose challenges. Many studies evaluating immunotherapy in early-stage breast cancer rely on surrogate endpoints such as pathological complete response rather than long-term outcomes such as disease-free or overall survival. While pCR is associated with improved prognosis in certain subtypes, it does not uniformly predict survival benefit across all patient populations. Additionally, variations in trial design, treatment regimens, biomarker assessment, and follow-up duration make it difficult to compare results across studies or establish standardized treatment protocols.

Economic and accessibility issues further limit the implementation of immunotherapy in early-stage breast cancer. Immune checkpoint inhibitors are associated with high costs, placing a significant burden on healthcare systems and potentially limiting access in low- and middle-income settings. Cost-effectiveness analyses in early-stage disease are still emerging, and the financial implications of treating large numbers of patients with curative intent must be carefully considered. Ensuring equitable access to advanced therapies remains a critical challenge in global oncology care.

Finally, uncertainties remain regarding the optimal timing, duration, and sequencing of immunotherapy in combination with conventional treatments. The relative benefits of neoadjuvant versus adjuvant immunotherapy, the appropriate length of treatment, and the most effective integration with chemotherapy and radiotherapy are not yet clearly defined. Addressing these questions will require continued clinical research and long-term follow-up data[3,8].

In summary, while immunotherapy combined with conventional treatment modalities holds promise for improving outcomes in early-stage breast cancer, its clinical application is constrained by biological, clinical, and systemic limitations. Overcoming these challenges will depend on advances in biomarker development, improved trial design, careful assessment of long-term safety, and strategies to enhance cost-effectiveness and accessibility.**Future Perspectives**

Future research is expected to focus on refining patient selection through biomarker development, optimizing combination strategies, and determining the most effective timing of immunotherapy. The integration of molecular profiling, immune signatures, and circulating biomarkers may further enhance personalized treatment approaches. As evidence matures, immunotherapy may become an integral component of standard treatment for selected patients with early-stage breast cancer[2,7,12].

Conclusion

The integration of immunotherapy with conventional treatment modalities such as chemotherapy and radiotherapy represents a promising advancement in the management of early-stage breast cancer. Current evidence demonstrates improved pathological response rates and encouraging survival outcomes, particularly in immunogenic subtypes such as triple-negative breast cancer. While challenges remain, ongoing clinical trials and translational research continue to refine the role of immunotherapy in early disease. The combination of immune-based strategies with traditional treatments has the potential to improve long-term outcomes while maintaining acceptable safety profiles, marking an important step toward personalized oncology in early-stage breast cancer.

References

1. Adams S, Diamond JR, Hamilton E, et al. Atezolizumab plus nab-paclitaxel in the treatment of metastatic triple-negative breast cancer. *N Engl J Med*. 2018;379(22):2108–2121.
2. Burstein HJ, Curigliano G, Loibl S, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen consensus. *Ann Oncol*. 2019;30(10):1541–1557.

3. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2019;30(8):1194–1220.
4. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy in early triple-negative breast cancer. *N Engl J Med*. 2020;382(9):810–821.
5. Denkert C, von Minckwitz G, Darb-Esfahani S, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer. *Lancet Oncol*. 2018;19(1):40–50.
6. Emens LA. Breast cancer immunotherapy: facts and hopes. *Clin Cancer Res*. 2018;24(3):511–520.
7. Finn RS, Qin S, Ikeda M, et al. Atezolizumab in combination with chemotherapy for cancer treatment. *Lancet*. 2020;395(10217):183–194.
8. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunogenic cell death in cancer and infectious disease. *Nat Rev Immunol*. 2017;17(2):97–111.
9. Hammerl D, Smid M, Timmermans AM, et al. Breast cancer genomics and immune response. *Breast Cancer Res*. 2018;20(1):135.
10. Keenan TE, Tolaney SM. Role of immunotherapy in triple-negative breast cancer. *J Natl Compr Canc Netw*. 2020;18(4):479–489.
11. Loi S, Michiels S, Salgado R, et al. Tumor infiltrating lymphocytes are prognostic in early breast cancer. *J Clin Oncol*. 2014;32(27):2959–2966.
12. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in early-stage triple-negative breast cancer. *Ann Oncol*. 2020;31(6):781–789.
13. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. 2020;382(9):810–821.
14. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin*. 2023;73(1):17–48.
15. Zitvogel L, Kroemer G. Immunogenic cell death in cancer therapy. *Nat Rev Immunol*. 2017;17(2):97–111.