Impact of Taxane- and Anthracycline-Based Neoadjuvant Chemotherapy on Immunohistochemical Biomarker Expression in Locally Advanced Breast Cancer

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ABSTRACT

Introduction: Neoadjuvant chemotherapy (NAC) has become a standard therapeutic approach in locally advanced breast cancer (LABC). Beyond tumor downstaging, NAC may induce biological alterations in tumor molecular profiles, including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki67 expression. Changes in these biomarkers may influence molecular subtype classification, prognosis, and subsequent treatment strategies.

Methods: This manuscript presents a structured literature synthesis derived from the literature review chapter, integrating current evidence regarding NAC mechanisms, immunohistochemical assessment, and biomarker modulation after systemic therapy.

Results: Anthracycline- and taxane-based regimens exert cytotoxic effects through DNA intercalation, topoisomerase II inhibition, and microtubule stabilization[3]. Literature demonstrates that NAC may alter ER, PR, HER2, and Ki67 expression via clonal selection, epigenetic modulation, and tumor microenvironment changes[2,6]. Biomarker conversion may result in molecular subtype shifts, particularly toward more aggressive phenotypes such as triple-negative breast cancer (TNBC)[7].

Discussion: Changes in immunohistochemical expression following NAC have important clinical implications. Reassessment of biomarkers after treatment is essential for optimizing adjuvant therapy selection and individualized treatment planning

INTRODUCTION

Breast cancer remains the most frequently diagnosed malignancy in women worldwide and represents a major cause of cancer-related mortality[17]. In many developing countries, a significant proportion of patients present with locally advanced breast cancer (LABC),

characterized by large tumor size, regional lymph node involvement, and aggressive biological features.

Neoadjuvant chemotherapy (NAC) is administered before surgery to reduce tumor size, improve resectability, and increase the likelihood of breast-conserving surgery[17]. Achievement of pathologic complete response (pCR) after NAC is associated with improved recurrence-free survival (RFS) and overall survival (OS), particularly in HER2-positive and triple-negative subtypes[18].

Tumor biology in breast cancer is largely determined by immunohistochemical biomarkers including ER, PR, HER2, and Ki67[16]. These markers define molecular subtypes—Luminal A, Luminal B, HER2-enriched, and TNBC—which guide systemic therapy decisions[14]. Emerging evidence indicates that NAC may modify biomarker expression and consequently alter tumor molecular classification[2],[5].

LITERATURE REVIEW

Neoadjuvant Chemotherapy in Breast Cancer

NAC was initially introduced for inoperable tumors but has expanded to include operable disease[17]. The primary objectives include tumor downstaging, assessment of in vivo therapeutic response, and prognostic stratification based on pCR[18]. HER2-positive and TNBC subtypes demonstrate higher pCR rates compared with luminal subtypes[18].

Standard regimens combine anthracyclines and taxanes[3]. In HER2-positive disease, targeted agents such as trastuzumab are added to improve response rates[15]. NAC not only reduces tumor burden but also affects tumor biology and immune microenvironment.

Mechanism of Action of Anthracyclines and Taxanes

Anthracyclines (e.g., doxorubicin) intercalate DNA and inhibit topoisomerase II, resulting in DNA strand breaks and apoptosis[3]. Taxanes (e.g., paclitaxel, docetaxel) stabilize microtubules and prevent depolymerization, arresting cells in mitosis and inducing cell death[3].

The combination of these agents enhances cytotoxic efficacy by targeting different cell cycle pathways. Tumors with high proliferative activity (e.g., elevated Ki67) often demonstrate better chemotherapy responsiveness[16].

Immunohistochemistry in Breast Cancer

Immunohistochemistry (IHC) is fundamental in breast cancer classification[8],[9]. The technique has evolved from early immunofluorescence methods[9] to modern avidin–biotin complex systems[8].

- **ER and PR** are nuclear hormone receptors associated with estrogen-driven proliferation. Positive expression predicts benefit from endocrine therapy[2].
- **HER2** is a transmembrane tyrosine kinase receptor associated with aggressive disease but responsiveness to targeted therapy[15].
- **Ki67** reflects proliferative activity and serves as a prognostic and predictive marker[16].

HER2 assessment may require confirmatory fluorescence in situ hybridization (FISH) when equivocal[15]. Accurate evaluation of these markers is critical for molecular subtype classification[14].

Effect of NAC on Immunohistochemical Biomarkers

NAC may induce biomarker conversion through clonal selection and epigenetic mechanisms[2].

ER and PR Changes

Hormone receptor conversion after NAC has been documented[2]. Loss of ER/PR expression may reflect selective elimination of hormone-dependent clones or epigenetic silencing mechanisms[2]. Gain of receptor expression has also been reported, potentially expanding endocrine therapy options[2].

HER2 Changes

HER2 status modification following NAC has been described[4,5]. Loss of HER2 positivity may occur due to receptor degradation or selective survival of HER2-negative clones[5]. Such changes have implications for continuation of anti-HER2 therapy[4].

Ki67 Changes

Ki67 is among the most dynamic biomarkers following NAC[6]. A reduction in Ki67 correlates with improved survival outcomes[6,7]. Conversely, persistent high Ki67 after treatment may indicate chemoresistance and poorer prognosis[7].

Molecular Subtype Conversion

Alterations in ER, PR, HER2, and Ki67 may result in molecular subtype conversion[2,5]. Some tumors convert toward TNBC phenotype, potentially reflecting clonal evolution under therapeutic pressure[2]. Subtype changes significantly influence adjuvant therapy decisions[14].

DISCUSSION

NAC exerts both cytoreductive and biological effects. Anthracycline- and taxane-based regimens eliminate chemosensitive tumor clones while resistant subpopulations may survive[3]. This clonal selection mechanism likely explains observed changes in ER, PR, and HER2 expression[2,5].

Loss of hormone receptor expression may reduce endocrine therapy responsiveness[2]. HER2 status changes may alter eligibility for targeted therapy[4,5]. Ki67 reduction is generally associated with favorable prognosis, whereas persistent elevation signals residual aggressive disease[6,7].

Molecular subtype conversion underscores the necessity of reassessing biomarkers after NAC[14]. Without reevaluation, patients may receive suboptimal adjuvant therapy.

Therefore, NAC should be regarded not only as tumor-shrinking therapy but also as a biological modulator of tumor phenotype.

CONCLUSION

Neoadjuvant chemotherapy using anthracycline- and taxane-based regimens plays a central role in the management of locally advanced breast cancer. Beyond tumor reduction, NAC may significantly alter ER, PR, HER2, and Ki67 expression[2,5,6].

These biomarker changes can lead to molecular subtype conversion and have important implications for prognosis and adjuvant treatment planning[14]. Routine reassessment of immunohistochemical markers following NAC is strongly recommended to optimize individualized therapy.

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