Category III

Comparison of Clinical and Pathological Tumour Staging Following CDK4/6 Inhibitor-based Neoadjuvant Therapy in HR+/HER2− Breast Cancer

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Objective: CDK4/6 inhibitors are an established component of systemic therapy for hormone receptor-positive (HR+)/HER2− breast cancer, with proven efficacy in combination with endocrine therapy in both advanced and early-stage disease. Their role in the neoadjuvant setting is increasingly explored, particularly for patients in whom chemotherapy may be less appropriate. This study evaluated the impact of CDK4/6 inhibitor-based neoadjuvant therapy on clinical-to-pathological tumour stage conversion and assessed biological subtype modulation before and after treatment.

Materials and Methods: This retrospective analysis included 92 patients (96 tumours, including four multifocal or bilateral cases) treated at a high-volume multidisciplinary breast unit. All patients received a CDK4/6 inhibitor combined with endocrine therapy, most commonly aromatase inhibitors ± GnRH agonists, as neoadjuvant systemic treatment. Tumour biology was assessed using standard immunohistochemistry for estrogen receptor, progesterone receptor, and HER2, with molecular subtypes classified according to St Gallen 2019 criteria. Clinical tumour stage (initial T) was compared with final pathological stage (final T) to assess downstaging. Ki-67 proliferation indices were recorded on core biopsy and final pathology.

Results: Pathological complete response (pCR) was observed in five tumours (5.2%), including one breast in a bilateral case. At baseline, Luminal B was the predominant subtype (53.1%), followed by Luminal A (41.7%), with HER2-equivocal tumours accounting for 5.2%. Following neoadjuvant therapy, Luminal A increased to 76.0% while Luminal B decreased to 11.5%, indicating marked biological differentiation and enhanced endocrine responsiveness. One Luminal B tumour converted to a triple-negative phenotype. HER2-equivocal tumours ($n = 6$) persisted without further SISH confirmation. On core biopsy, only 10 patients demonstrated a Ki-67 ≤6%. Post-treatment pathology revealed a substantial reduction in proliferative activity, with 53 patients showing Ki-67 <3%, including four with <1%. A parallel reduction in tumour size and stage was observed, with most tumours demonstrating downward T-stage migration (e.g., T3-T4 to T1-T2).

Conclusion: CDK4/6 inhibitor-based neoadjuvant therapy results in meaningful tumour downstaging and biological subtype modulation in HR+/HER2− breast cancer. The frequent conversion from Luminal B to Luminal A and the marked suppression of Ki-67 support the cytostatic, differentiation-driven mechanism of CDK4/6 inhibition. Although pCR rates remain modest compared with chemotherapy, the consistent biological and morphological responses highlight this approach as a lower-toxicity alternative or complement to chemotherapy in selected patients. Prospective studies incorporating proliferative dynamics and nodal outcomes are warranted.

Keywords: Staging; South Africa; HR+/HER2