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Different effects of tamoxifen and exemestane on cognitive functioning of postmenopausal patients with early breast cancer: results from the Dutch TEAM neuropsychological side study

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Background: Research indicates that estrogens are neuroprotective and improve certain cognitive functions, but also suggests that estrogen replacement therapy increases dementia-risk in women >65 yrs of age. Due to their anti-estrogenic properties, endocrine therapies (ET) for breast cancer (BC) might also influence cognition, but few studies have examined this safety aspect. Cognitive effects of ET might also be age-dependent. Due to different mechanisms of action, differential cognitive effects between selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) are possible.
Materials and Methods: Patients (pts) were Dutch women participating in the TEAM-trial, a randomized study investigating tamoxifen (SERM) versus exemestane (AI) as adjuvant therapy for hormone-sensitive postmenopausal BC. Cognitive tests covering 8 cognitive domains were performed before the start of ET (T1) and after 1 year of ET (T2) in pts not being treated with chemotherapy. The study sample consisted of 80 tamoxifen users (mean age 68.7 yrs, range 51−84) and 99 exemestane users (mean age 68.3 yrs, range 50−82). A healthy control group (n = 120, mean age 66.2 yrs; range 49−86) was assessed with a similar interval. Performance at T2 on 8 cognitive domains was compared between the 3 groups by use of ANCOVA adjusting for performance at T1 and anxiety/depression, fatigue and menopausal symptoms. The analyses were repeated for younger ($\leqslant$65 yrs) and older (>65 yrs) participants separately.
Results: At T2, younger and older exemestane users did not perform significantly worse than healthy women on any cognitive domain. Tamoxifen users performed worse than healthy controls on verbal memory ($P = 0.006$, Cohen's d = 0.40) and executive functioning ($P = 0.005$, Cohen's d = 0.41) and worse than exemestane users on information processing speed ($P = 0.02$, Cohen's d = 0.36). Compared with healthy controls, younger tamoxifen pts performed worse on 'executive functioning' ($P = 0.01$, Cohen's d = 0.54), while older tamoxifen pts performed worse on 'verbal memory' ($P = 0.003$, Cohen's d = 0.58) and 'information processing speed' ($P = 0.03$, Cohen's d = 0.44).
Conclusions: After one year of therapy, tamoxifen has a negative effect on certain cognitive functions in postmenopausal BC patients, while exemestane does not negatively affect cognition in this population. Tamoxifen might have a differential effect on cognition in various age groups. Our results underscore the need to include potential cognitive effects of ET in long-term safety studies.

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Estrogen and progesterone receptor as predictive biomarkers of response to endocrine therapy: a prospectively powered pathology study in the tamoxifen and exemestane adjuvant multinational (TEAM) trial

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Background: The Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial included a prospectively planned pathology substudy testing the predictive value of progesterone receptor (PgR) expression for outcome of estrogen receptor-positive (ER+) early breast cancer patients treated with exemestane versus tamoxifen.
Patients & Methods: Pathology blocks from 4781 TEAM patients randomized to exemestane versus tamoxifen followed by exemestane for 5 years of total therapy were collected centrally and tissue microarrays constructed from 4598 cases. Quantitative analysis of hormone receptors (ER and PgR) using image analysis and immunohistochemistry were performed, linked to outcome data from the main TEAM trial, and analyzed relative to disease-free survival and treatment.
Results: Of 4325 eligible ER+ cases, 23% were PgR-poor (Allred $\leqslant$4) and 77% were PgR-rich (Allred $\geqslant$5). No treatment by marker effect for PgR was observed for exemestane versus tamoxifen (PgR-rich hazard ratio [HR], 0.81; 95% CI, 0.63−1.03; PgR-poor HR, 0.84; 95% CI, 0.60−1.17; $P = 0.85$ for interaction). Both PgR and ER expression were associated with patient prognosis (DFS) in univariate (PgR HR, 0.52; 95% CI, 0.43−0.64; $P < 0.0001$; ER HR, 0.66; 95% CI, 0.51−0.85; $P = 0.001$) and were independent prognostic variables in multivariate analyses ($P < 0.0001$ and $P = 0.0054$, respectively). No interaction between the prognostic impact of ER and PgR was observed. A trend toward treatment by marker effect for ER-rich cases was observed.
Conclusion: Preferential exemestane versus tamoxifen treatment benefit was not predicted by PgR expression; conversely, patients with ER-rich tumors may derive additional benefit from exemestane. Both ER and PgR quantative expression were linearly and independently associated with relapse risk and could influence patient treatment choices if included in risk-benefit comparisons of aromatase inhibitors versus tamoxifen.

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The need for a biological grading system and its relationship to the current Nottingham histological grading system (NGS)

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Background: In this study, we hypothesised the interaction between mitotic index; MI and Bcl2, could accurately discriminate between low and high-grade breast cancer (BC) and provide a more objective and clinically valuable measure of tumor grade with prognostic significance for patients with moderately differentiated cancer.
Material and Methods: A series of 1585 invasive BC with long term follow up were immunohistochemically profiled for apoptosis regulators and others. Mitotic index was assessed according to NGS: M1; <10 mitoses, M2; 10 to 18 mitoses and M3; >18 mitoses. Subsequently, BC were classified according to combined MI/Bcl2 profile and compared to NGS.
Results: In multivariate Cox regression models including validated prognostic factors, the MI/Bcl2 profile not only remained significantly associated with patients' outcomes but performed better than lymph node status and tumour size. Incorporation of the MI/Bcl2 profile into NPI, accurately reclassified twice as many patients into excellent (EPG) or poor prognostic groups (PPG), improving decision-making for which patients should be given systemic adjuvant therapy. Patients with M1/Bcl2$\pm$ and M2/Bcl2+ (NGS G1 like) produced a better response to hormone therapy than those with M2−3/Bcl2− and M3/Bcl2+ (NGS G3 like) (HR 3.4; $p < 0.0001$).
Conclusion: Biological grading achieved through mitosis and Bcl2 expression reclassified the majority (70%) of patients with equivocal NGS G2 into two groups NGS G1 like with low risk versus NGS G3 like with high risk of recurrence, improving prognosis and therapeutic planning and supporting the genetic pathway model of tumour grade origin.