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Adjuvant Therapy With Zoledronic Acid in Primary Breast Cancer: a Systematic Review and Meta-analysis

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Background: The purpose of this study is to address the role of zoledronic acid in breast adjuvant setting treatment as an antitumour agent and as a preventive therapy against bone fractures.
Materials and Methods: We performed a systematic review and meta-analysis of randomized clinical trials. Trials were located through PubMed, ISI, Cochrane Library and major cancer scientific meetings searches. All trials that randomized patients with primary breast cancer to undergo adjuvant treatment with zoledronic acid versus non-use, placebo, or delayed use of zoledronic acid as treatment to individuals who develop osteoporosis were considered eligible. Standard meta-analytic procedures were used to analyze the study outcomes. Study protocol has been registered on International Prospective Register of Systematic Reviews (PROSPERO, CRD Register 2011: CRD42011001179).
Results: Twelve studies were considered eligible with 8469 analyzed patients. The use of zoledronic acid resulted in a statistically significant improvement of overall survival (5 studies, 6414 patients, Hazard Ratio [HR] 0.82, 95% Confidence Interval [CI] 0.70–0.95, p = 0.009). No difference were found for disease-free survival (7 studies, 7541 patients, HR 0.86, 95% CI 0.69–1.08, p = 0.2) or overall recurrence (8 studies, 7644 patients, Odds Ratio [OR] 0.91, 95% CI 0.80–1.03 p = 0.12). Zoledronic acid treatment resulted in lower bone metastasis rate; nonetheless this difference did not reach statistal significance. (8 studies, 7644 patients, OR 0.83, 95% CI 0.67–1.02 p = 0.08). Finally treatment with zoledronic acid did not reduce the fracture rate (8 studies, 4830 patients, OR 0.86 95% CI 0.65–1.15, p = 0.31). Considering zoledronic acid-specific adverse events, osteonecrosis of the jaw was observed in 24 of 4419 patients (0.54%) who received zoledronic acid.
Conclusion: Zoledronic acid as adjuvant therapy in primary breast cancer appears to offer a survival benefit compared to placebo or no treatment. Nonetheless, further research is essential, in order to confirm our findings and substantiate its potential benefit of zoledronic acid as an antitumour agent in the adjuvant setting.

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Specific Adverse Events and Outcome in Hormone Receptor Positive Breast Cancer Patients on Endocrine Therapy − a TEAM Study Analysis

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Background: It has been suggested that occurrence of specific adverse events (AE) during adjuvant endocrine therapy may affect breast cancer (BC) outcome [1]. Others propose however that AE may simply reflect therapy adherence, and thereby improve outcome. Aim of this study was to assess presence of adverse events within three months after start of adjuvant endocrine therapy, and to evaluate breast cancer recurrence according to presence of AE within three months.
Materials and Methods: Overall 9766 postmenopausal women enrolled in the TEAM trial, were randomized to either exemestane (25 mg daily) for 5 years or tamoxifen (20 mg daily) for 2.5−3 years, followed by exemestane for 2−2.5 years. Adverse events were categorized as none, specific, or non specific. Specific AE were defined as vasomotor and joint symptoms [1]. Non specific AE included all other AE as earlier reported in the TEAM efficacy analysis [2]. Relapse free period was defined as time to earliest documentation of disease relapse or death due to breast cancer.
Results: In the present study 9597 patients were included. Overall, 24% reported a specific, 14% a non specific, and 62% no adverse event within the first three months. Presence of specific AE within three months decreased with increasing age, while presence of non specific AE was not affected by age (p < 0.001). Univariate analysis showed an improved relapse free period for specific and non specific AE compared to patients without AE (p = 0.006) (Table 1). In multivariable analysis, adverse events were not associated with relapse free period (overall p = 0.974). Patients reporting specific adverse events had a similar relapse free period as patients reporting a non specific adverse event (HR 0.94 (0.73–1.21), p = 0.652).
Conclusions: This study did not confirm an earlier report of higher recurrence free survival for patients who reported specific AE. The present data show that patients with either specific or non specific AE within three months have a similar breast cancer outcome. Report of AE in general therefore might reflect patient characteristics rather than a biological mechanism.

Table 1. Relapse free period

		Univariate analysis		Multivariable analysis*	
	5 y%	HR (95% CI)	p value	HR (95% CI)	p value
AE <3 months		**0.006**		**0.974**	
None	88	1 (ref)		1 (ref)	
Specific	90	0.79 (0.67–0.92)		1.02 (0.83–1.25)	
Non specific	90	0.85 (0.70–1.02)		0.99 (0.84–1.18)	

*HR adjusted for country, histological grade, T stage, nodal stage, and age.

References

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A Randomized Study Comparing Standard to Response-adapted Sequence in HER2 Negative Operable Breast Cancer

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Purpose of the study: Pathological complete response (pCR) has been widely used as a surrogate marker in NACT. This study was designed to evaluate the role of adapting the treatment to changes seen from outsides at the tumour level. PCR rates will be studied comparatively in 264 BC women, stage II-IIIA operable, who randomized to receive either 3 FEC 100 then 3 docetaxel 100 mg/m^2 (standard arm A), or adapted arm B beginning with 2 FEC 100. Docetaxel will be given if tumour size decreased by less than 30 or 50 percent after 2 or 4 FEC 100, respectively; otherwise FEC100 was given for 6 courses before surgery. A new classification will assess the limited residual disease in breast and nodes (LRDBN) when obtained.
Patients and Methods: 145 patients, all Her 2 negative with or without HR on microbiopsies, have been randomized to date with a median age of 52 years. This intermediary intent to treat analysis was carried out in 115 operated patients: 58 patients in arm A (47 luminal; 11 TN) and 57 patients in arm B (47 luminal; 10 TN). PCR rate has been analysed according to Chevallier's (Am J Clin oncol 1993) and Sataloff's (J Am Coll Surg 1995) classifications. A retrospective analysis of pathology was carried out in 41 patients, who had a small residual tumour, in order to assess the "new pCR" named LRDBN, reached when 4 criterias were met: Ki 67(<5%), tumour surface residual vs initial (<5%), large tumoral fibrosis/elastosis and node metastasis ($\leqslant$2 mm).
Results: Objective response rate was 48% in arm A (L: 40%; TN: 82%) versus 54% in arm B (L: 47%; TN: 90%). The pCR rate was 14% in arm A (L: 6%; TN: 45%) vs 14% in arm B (L: 4%; TN: 60%) for Chevallier (1 + 2 classes); 16% in arm A (L: 6%; TN: 55%) vs 19% in arm B (L: 11%; TN: 60%) for Sataloff (TANA + TANB); 19% in arm A (L: 11%; TN: 55%) vs 21% in arm B (L: 13%; TN: 60%) patients achieved pCR according to the new classification, LRDBN.
Conclusion: TN tumours responded better to NACT than luminal phenotype. A high pCR rate according to Chevallier's and Sataloff's was obtained in 60% of TN subgroup patients with the response-adapted strategy. Trial must go on to reach its final goal.