Zoledronic acid improves disease-free survival in premenopausal HR+ early breast cancer

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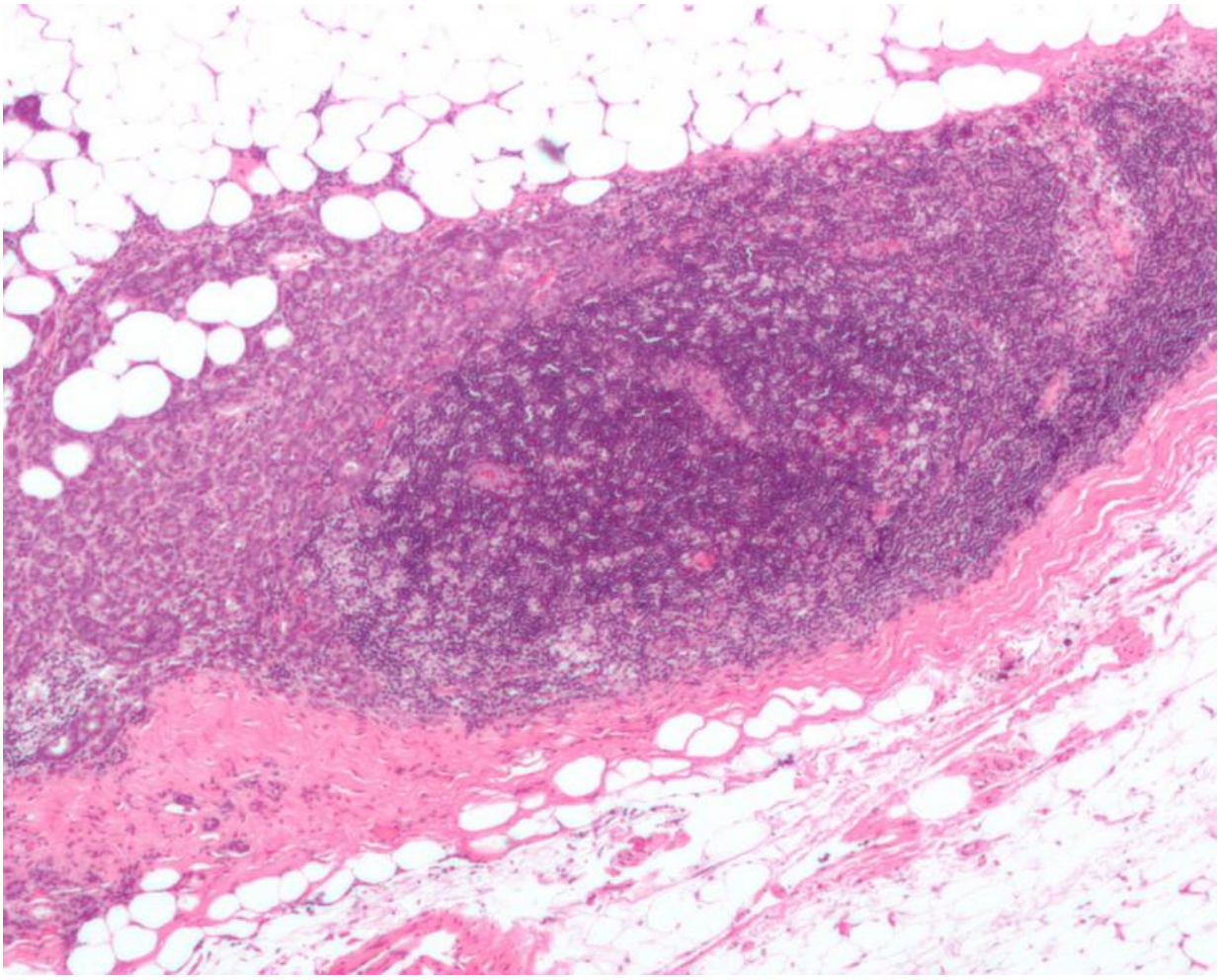

Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

Adjuvant treatment with the bone sparing drug zoledronic acid plus hormonal therapy with the aromatase inhibitor letrozole significantly increases disease-free survival compared to tamoxifen in premenopausal women with hormone receptor positive (HR+) early breast cancer, according to results reported at ESMO 2018 Congress in Munich. It is the first study to assess this specific combination in premenopausal breast cancer and adds to previous observations with zoledronic acid and anastrozole in premenopausal women receiving ovarian suppression.

Studies have shown reduced recurrence and breast cancer mortality with zoledronic acid plus hormonal therapy in HR+ breast cancer in postmenopausal women, but the benefit in premenopausal women was previously less clear. Zoledronic acid is a bisphosphonate that reduces the rate of bone turnover; it is licensed to treat osteopororosis and to reduce bone damage in advanced cancers involving bone and hypercalcaemia in cancer. Unlike tamoxifen, which blocks estradiol binding to the estrogen receptor, letrozole is an aromatase inhibitor that profoundly suppresses estradiol levels but has not previously been evaluated in premenopausal breast cancer.

The HOBOE-2 (Hormonal BOne Effects-2) phase 3 trial included 1065 patients with estrogen/progesterone receptor positive early breast cancer who had their last period within one year of randomisation. They were treated with the gonadotrophin-releasing hormone agonist triptorelin (3.75mg every four weeks) for five years up to the age of 55 to suppress ovarian function and nearly two-thirds (63%) received chemotherapy before randomisation.

The patients were randomised to hormonal therapy with tamoxifen (20mg/day) or letrozole (2.5mg/day) or to combination therapy with zoledronic acid (4mg IV every six months) plus letrozole (2.5mg/day) (ZL) for a planned treatment duration of five years. The study was stopped early in May 2018 after a median follow-up of 65 months when

the Independent Monitoring Committee recommended sharing the data with the Early Breast Cancer Trialists' Cooperative Group (EBCTCG) 2018 overview.

Results reported at ESMO 2018 showed there were 32 breast cancer recurrences or second breast or non-breast cancers or deaths in patients treated with ZL, giving a 5-year disease-free survival (DFS) probability of 0.93. There were 58 events in patients treated with tamoxifen and 44 events in the letrozole group, giving 5-year DFS event rates of 0.85 and 0.93, respectively (p=0.008).

Disease-free survival was significantly improved in patients randomised to zoledronic acid plus letrozole compared to those treated with tamoxifen, with an absolute advantage of 8% in 5-year DFS. The risk of breast cancer recurrence or non-cancer death was nearly halved in patients treated with ZL compared to those treated with T (hazard ratio [HR] 0.52, 95% confidence interval 0.34-0.80, p=0.003).

The improvement in DFS with ZL compared to tamoxifen was seen in all subgroups of patients apart from the small subgroup of women with tumours overexpressing HER2 who showed greater benefit with tamoxifen (interaction p=0.002).

There was no statistically significant difference in DFS comparing letrozole with tamoxifen (HR 0.72, 95% CI 0.48-1.07, p=0.06) or comparing ZL with letrozole alone (HR 0.70, 95% CI 0.44-1.12, p=0.22).

As expected, side-effects were more frequent in patients treated with ZL, with 9% of patients experiencing grade 3-4 toxicity compared to 4% of those treated with T and 7% of those treated with L. Nearly one in five (17%) patients treated with ZL stopped treatment before 5 years due to toxicity or refusal, compared to 7% of those on T and 7% of

those on L. Among the most feared side-effects associated with the study drugs, there were four cases of jaw osteonecrosis in the ZL arm.

"HOBOE-2 strongly supports the hypothesis that combination treatment with an aromatase inhibitor and bisphosphonate plus triptorelin may improve prognosis in premenopausal patients with HR-positive breast cancer," said lead author Prof. Francesco Perrone, Director of the Clinical Trials Unit at the Istituto Nazionale Tumori, Naples, Italy.

Perrone continued: "We had previously shown that, in combination with triptorelin, letrozole suppresses estradiol levels much more than tamoxifen in premenopausal patients. And we know that suppressing estradiol levels means cutting the fuel to endocrine-dependent breast cancer."

Considering zoledronic acid, Perrone said: "Our hypothesis is that the drug modifies the bone microenvironment that is the niche where breast cancer micrometastases remain in a state of dormancy, potentially for many years. Microenvironment modifications may be lethal for isolated cancer cells, reducing the risk of distant metastases over time." He explained: "The two mechanisms are partially independent and, therefore, may sum up to give an additive benefit."

Reviewing the potential impact on clinical practice, Perrone suggested: "If the size of the benefit we saw is confirmed with longer follow-up, ZL treatment might turn out to be a highly cost-effective treatment for premenopausal HR+ breast cancer." He noted that zoledronic acid and letrozole are both very cheap drugs, so could be used widely.

Commenting on the study for ESMO, Robert Coleman, Emeritus Professor of Medical Oncology, University of Sheffield, UK, said: "The findings add to existing information to support the use of more intensive treatment with an aromatase inhibitor and bisphosphonate in women at

high risk for recurrence, either by virtue of node involvement or high-grade or large tumours." He noted: "Both treatments add toxicity over and above tamoxifen and so are best limited to women at intermediate to high risk where the risk-benefits are likely to be acceptable."

Coleman cautioned that the study was underpowered, with insufficient events for statistical confidence in the results. He added: "This study is not definitive but adds to the information on these two treatment approaches and will contribute to the ongoing EBCTCG meta-analyses." He considered there were unlikely to be further trials with aromatase inhibitors and bisphosphonates as the focus is now on adding other targeted treatments.

More information: Abstract LBA14_PR 'The HOBOE-2 multicenter randomised phase 3 trial in premenopausal patients with hormone-receptor positive early breast cancer comparing triptorelin plus either tamoxifen or letrozole or letrozole + zoledronic acid' will be presented by Francesco Perrone during the Poster Discussion session on Saturday 20 October, 15:00 to 16:15 (CEST) in Room 15—Hall A1. *Annals of Oncology*, Volume 29 Supplement 8 October 2018

Gnant M, Mlineritsch B, Schippinger W et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *NEJM* 2009; 360: 679-691

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