Extended adjuvant bisphosphonate treatment over five years in early breast cancer does not improve disease-free and overall survival compared to two years of treatment: Phase III data from the SUCCESS A study

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Background:
A recent meta-analysis has reported benefits of adjuvant bisphosphonate treatment in early breast cancer patients with improved breast cancer survival and reduced rate of breast cancer recurrences in the bone, especially in postmenopausal patients. However, a comparison between bisphosphonate treatments duration is lacking. Therefore, we examined 2 and 5 years of zoledronate treatment following adjuvant chemotherapy in the SUCCESS A trial.

Methods:
The SUCCESS A trial is a randomized, open-label, 2x2 factorial design Phase III study in high-risk early breast cancer patients that were randomized to adjuvant chemotherapy treatment with 3 cycles of FEC followed by either 3 cycles of docetaxel or 3 cycles of gemcitabine-docetaxel. After chemotherapy, patients were subject to a second randomization of 5 years of zoledronate treatment (4 mg i.v. every 3 months for 2 years, followed by 4 mg i.v. every 6 months for 3 years) vs. 2 years of zoledronate treatment (4 mg i.v. every 3 months for 2 years). Outcome was analyzed using adapted disease-free survival (DFS) and adapted overall survival (OS), with survival times measured as of 2 years after the start of zoledronate treatment. Maximal observation time was set to 4 years. Median observation time was 2.95 years for DFS and 3 years for OS.

Results:
Overall, 3421 of the 3754 patients randomized in the SUCCESS A study received at least one zoledronate dose. 434 patients had a DFS event or were lost to follow up in the first two years after the start of zoledronate treatment; thus, 2987 patients were available for analysis (1540 and 1447 patients in the 5-year and 2-year zoledronate treatment arm, respectively). Both adapted DFS and adapted OS did not differ between the two treatment arms (5 vs. 2 years) as shown by multivariate cox regressions adjusted for patient and tumor characteristics as well as chemotherapy (DFS: hazard ratio [HR] 0.97, 95% confidence interval [CI] 0.75 – 1.25, p = 0.81; OS: HR 0.98, 95% CI 0.67 – 1.42, p = 0.90). In addition, subgroup analyses according to menopausal status revealed no difference in DFS or OS between the two treatment arms in premenopausal women (DFS: HR 1.21, 95% CI 0.81 – 1.81, p = 0.35; OS: HR 0.93, 95% CI 0.57 – 1.53, p = 0.78) or postmenopausal women (DFS: HR 0.85, 95% CI
Conclusions:
Our study showed no difference in DFS or OS between 5-years and 2-years of adjuvant zoledronate treatment in early breast cancer patients, irrespectively of menopausal status. Thus, our results indicate that extended treatment with zoledronate does not improve DFS or OS in high-risk early breast cancer patients.