short review

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The ASCO 2018 annual meeting: update on the adjuvant treatment of early breast cancer

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Summary At this year's American Society of Clinical Oncology (ASCO) annual meeting two large phase 3 trials, the ABCSG-18 and the D-CARE study, analysed the effects of adjuvant denosumab in breast cancer patients and reported different outcomes. Another phase 3 study, the ASTRRA trial, investigated the use of adjuvant ovarian function suppression (OFS) in high-risk premenopausal patients. This trial confirmed the benefit of OFS similar to the results of the already published SOFT/TEXT trials but raises some crucial questions on the optimal duration of OFS in these patients. The results of the SOFT/TEXT trials were also updated at this meeting.

Keywords Bisphosphonates · Endocrine therapy · Bone-modifying agents · Denosumab · Ovarian function suppression

Denosumab as adjuvant treatment for early breast cancer

Most data concerning the adjuvant use of bone-modifying agents are derived from trials investigating bisphosphonates. As the results of these trials are conflicting, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted a meta-analysis of 18,766 individual patient datasets provided by 26 randomised, controlled trials recording recurrence.

Bone recurrence and breast cancer mortality were significantly reduced in the entire study population, comprising pre- and postmenopausal women receiving bisphosphonates, compared to the control group. However, subgroup analyses revealed that treatment had no apparent effect on any outcome in premenopausal women. While the benefit for bisphosphonates was consistent across all subgroups of postmenopausal patients, including overall survival (OS), the absolute benefit was rather limited [1]. Based on these results the American Society of Clinical Oncology (ASCO) limited recommendations for the adjuvant use of bisphosphonates in postmenopausal patients to those patients who—based on high risk of recurrence—would also receive adjuvant systemic therapy [2].

Two trials, investigating the adjuvant use of the anti-RANK ligand antibody denosumab, the ABCSG-18 [3] and the D-CARE [4] study, reported on their outcomes.

In ABCSG-18, a prospective, double-blind, placebo-controlled phase 3 trial, 3425 postmenopausal women with non-metastatic, hormone receptor-positive (HR+) breast cancer receiving adjuvant treatment with non-steroidal aromatase inhibitors (AI) were enrolled. Postmenopausal status was defined as being 60 years of age or older, having undergone bilateral oophorectomy, or being younger than 60 years with follicle-stimulating hormone (FSH) and estradiol levels in the postmenopausal range.

In all, 3420 patients were randomly assigned in a 1:1 ratio to receive either denosumab 60 mg or matching placebo subcutaneously every 6 months. Of these, 2468 (72.2%) had tumours up to two centimetres, 2436 (71.2%) had node-negative disease, 642 (18.8%) had poorly differentiated cancers (G3), 216 (6.3%) had human epidermal growth factor receptor 2 (Her2) positive disease and only 845 (24.7%) had received (neo)adjuvant chemotherapy prior to

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randomisation—thus comprising a good risk patient population [3, 5].

Vertebral x-ray and dual-energy x-ray absorptiometry (DXA) were performed at baseline and months 12, 24, 36 and at the end of study visit, respectively. Bone scans were only carried out at baseline and if bone metastasis was suspected at any point throughout the study.

Time from randomisation to first clinical fracture, the study's primary endpoint, was significantly delayed and the benefit even increased over time in the denosumab group compared with the placebo group (hazard ratio [HR] = 0.5, $p < 0.0001$) and has previously been published [5].

Disease-free survival (DFS), one of the secondary endpoints, was defined as time from randomisation to any evidence of local/regional or distant recurrence, contralateral breast cancer, secondary carcinoma or death from any cause and was analysed by intent-to-treat. After a median follow-up of 72 months a significant improvement of DFS (HR = 0.82, Cox $p = 0.026$) could be observed in the denosumab group. Sensitivity analyses demonstrated that adjustment for treatment cross-over and bone-targeted therapy only marginally influenced the results. The absolute benefit was approximately 2% at five and 3% at eight years of follow-up. At this point, it appears that the DFS benefit is not driven by local/regional or non-invasive recurrence or by contralateral breast cancer. However, this observation is still unreliable and will require longer follow-up.

The incidence of adverse events (AE) in all patients receiving at least one dose of study drug did not differ between the two groups nor did the incidence of serious adverse events (SAE, 30% both groups). With longer follow-up no new safety signals occurred. No case of osteonecrosis of the jaw (ONJ) was reported. Denosumab at 60 mg every six months did not add any toxicity to AI therapy [3].

D-CARE, an international, prospective, placebo-controlled, double-blind phase 3 trial, included 4509 patients, of whom 2149 (48%) were postmenopausal, with stage II and III early breast cancer, scheduled to receive standard of care (neo)adjuvant systemic and locoregional therapy with no more than 12 weeks between definitive surgery and randomisation.

Computed tomography (CT) scans of chest, abdomen and pelvis and bone scans were performed annually to screen for recurrence, which was determined by an independent blinded review panel.

Patients were randomised 1:1 to receive denosumab at a dose of 120 mg subcutaneously every 3–4 weeks for six cycles alongside adjuvant chemotherapy, followed by the same dose every three months for a total of five years or matching placebo at the same schedule.

Of all the included patients, 4215 (93.5%) had node-positive disease, 1844 (40.9%) had poorly differentiated tumours (G3), 3492 (77.4%) had HR+, 905 (20%) Her2 positive and 684 (15.2%) triple-negative tumours and a total of 4321(95.9%) received (neo)adjuvant chemotherapy and 1898 (42%) adjuvant AI therapy—thus comprising a fairly high-risk patient population.

After a median follow-up of 67 months, the trial's primary endpoint bone metastasis-free survival (BMFS), a composite endpoint, showed no difference between the treatment groups. However, only 255 patients (43%), who met the primary endpoint, had their first relapse in bone. There was no subgroup that seemed to benefit. Even menopausal status showed no interaction with treatment effect. For DFS, which did not include non-breast cancer new primaries, a numerical decrease of bone metastases with denosumab was observed; however this effect was counteracted by an excess number of recurrences in the opposite breast or at distant non-bone sites. Overall, the trial could not demonstrate any difference for DFS or OS between treatment groups. In the exploratory analyses, denosumab prolonged the time to bone metastasis as site of first recurrence, the time to first on-study fracture- (HR = 0.76, $p = 0.004$) and skeletal-related event following bone metastasis.

Overall, safety events did not differ much within the two groups with only slightly more SAE in the denosumab group which was mainly driven by the incidence of ONJ (5.4 vs 0.2%) with this intense regime. However, no difference was seen in terms of new primary malignancies [4].

As ABCSG-18 has not reported on BMFS or OS and as both studies have not been fully published yet, these differing results should be interpreted with great caution. The higher rate of ONJ can probably be attributed to the more intense dosing regimen used in D-CARE. The differences in DFS seen in the two studies might be explained by the different patient populations, both in terms of menopausal status and breast cancer risk. While in a clinically good risk, strictly HR+ postmenopausal patient population a significant improvement in DFS could be demonstrated, no effect could be observed in a high-risk population, not even in the postmenopausal subset. While in D-CARE secondary non-breast malignancies, which were calculated as safety events, appeared not to be affected by the addition of denosumab, ABCSG-18, which counted them as DFS events, reported their reduction. Whether this difference has significantly influenced the outcomes of the two trials yet remains unclear.

Ovarian function suppression in the adjuvant treatment of high-risk premenopausal women

The addition of ovarian function suppression (OFS) to either adjuvant tamoxifen or exemestane in the treatment of premenopausal women at high risk of breast cancer recurrence has been established based on the results of the SOFT and TEXT trials. The SOFT

trial randomly assigned 3066 patients with HR+ breast cancer to 5 years of exemestane plus OFS (E+OFS), tamoxifen plus OFS (T+OFS) and tamoxifen alone. The TEXT study allocated 2672 patients to 5 years of E+OFS or T+OFS. In both trials, randomisation was stratified according to the receipt of chemotherapy (1636 [53%] in SOFT, 1592 [60%] in TEXT). In the TEXT trial, chemotherapy, if administered, was started concomitantly with OFS. Endocrine therapy was added after chemotherapy had been completed. In SOFT, patients who received chemotherapy prior to randomisation and remained premenopausal were enrolled within 8 months after completing chemotherapy, once a premenopausal estradiol level was confirmed. The improvement of DFS and OS by the addition of OFS to tamoxifen as well as the prolongation of breast cancer and distant recurrence-free interval with E+OFS vs T+OFS have previously been published [6–9].

For each of the 4891 HR+, Her2-negative patients (86% of the total SOFT/TEXT population) included in the analysis of the absolute improvement in 8-year distant recurrence-free interval (DRFI) a previously defined continuous composite recurrence risk index (CRI), derived from clinicopathological characteristics [8], was calculated and stratified by 4 cohorts, defined by trial and chemotherapy use, and treatment assignment.

Overall 8-year DRFI was 91% and ranged from approximately 100 to 63% across lowest to highest CRI. DFRI, as expected, was lower in the chemotherapy than the endocrine-only groups. In TEXT patients, DRFI was 92% with a median CRI of 1.7 and the absolute benefit of E+OFS vs T+OFS was 3% (0–15% across CRI values).

DRFI in SOFT patients who did not receive chemotherapy (median CRI 1.1) was excellent across treatment groups and the additional benefit of OFS was marginal. In the SOFT chemotherapy group, however, with a higher median CRI of 2.1, improvement of E+OFS vs tamoxifen ranged from 2–10% and from 0–5% with T+OFS vs tamoxifen alone, respectively [10].

Overall, the results of the DRFI analysis at 8 years are in line with previously published data [6–9] showing that the higher the patient's risk of recurrence, the more absolute benefit can be gained from the addition of OFS even above the potential benefit of chemotherapy [10].

The ASTRRA trial, a prospective, randomised phase 3 study conducted in Korea, enrolled 1483 premenopausal patients ≤45 years of age with stage I–III HR+ breast cancer. This study focused on the effect of adding OFS to tamoxifen in a high-risk group, as only patients for whom the risk of recurrence was deemed high enough to indicate (neo)adjuvant chemotherapy could be enrolled. This resulted in a trial population with 55% node-positive patients and a low median age of 40 years.

Within 3 months of completion of chemotherapy, preservation of premenopausal status was confirmed by FSH levels <30 mIU/ml. In case of chemotherapy-induced amenorrhea, patients received oral tamoxifen and evaluation of menstrual status (FSH measurement and menstruation history within 6 months) was repeated every 6 months for up to 2 years after enrolment. Only 154 patients (11%) were premenopausal within 3 months after completion of chemotherapy. A vast majority regained premenopausal status within 6 months, but still a significant proportion did so between 6 months and 2 years after enrolment. In this very young population very few patients (approximately 6%) did not resume ovarian function.

Overall, 1282 premenopausal patients were randomly assigned 1:1 to 5 years of tamoxifen with or without OFS by monthly goserelin for 2 years.

After a median follow-up of 63 months, DFS (local/regional or distant recurrence, contralateral breast cancer, secondary malignancy or death by any cause) at 5 years, the trial's primary endpoint, was 91.1% in the T+OFS and 87.5% in the tamoxifen group (HR = 0.69, $p = 0.033$). Subgroup analyses were quite consistent. Only in the subgroup of tumours below 2 centimetres did the point estimate favour tamoxifen alone, although this might be due to the very low event rate in this subgroup. OS, the key secondary endpoint, was also significantly improved at 5 years by the addition of OFS (HR = 0.31, $p = 0.029$) [11].

Based on these results, ASTRRA confirms the previously published data from SOFT/TEXT [6–9] as the 5-year DFS and OS were significantly improved in a high-risk breast cancer population ≤45 years of age with the addition of OFS to tamoxifen. However, these results raise the question whether 2 years of OFS might be enough to generate this benefit. Most importantly, this trial points out that monitoring of ovarian function recovery should be at least carried out until 2 years after completion of chemotherapy in such a young patient population as a significant proportion of patients resumed ovarian function beyond 6 months after chemotherapy.

Take home message

The reduction of treatment-related fractures observed with denosumab in ABCSG-18 was confirmed by D-CARE, although the effect appeared to be smaller, which might be explained by the less frequent use of AI in this study. Data on DFS are however rather conflicting. While denosumab improved DFS in a low-risk, strictly HR+ postmenopausal population, no benefit could be observed in patients at high risk of recurrence.

When discussing the preferred option of adjuvant bone-modifying agent, one should consider that, despite the contradictory DFS results of the denosumab trials, the hazard ratio for DFS in ABCSG-18 is rather comparable to the one reported in the EBCTCG meta-

analysis for bisphosphonates in postmenopausal patients. However, while OS is still immature in ABCSG-18, bisphosphonates demonstrated an improvement in breast cancer specific and overall survival.

ASTRRA confirmed the DFS and OS benefit of the addition of OFS in high-risk premenopausal women observed in the SOFT/TEXT trials. However, in this study 2 years of OFS were sufficient to generate that benefit, raising the question on the optimal duration of adjuvant OFS. At this point, OFS for 5 years should be the standard of care; however, in case of poor tolerability omission after a minimum of 2 years seems feasible. Extended re-evaluation of the menopausal status after chemotherapy may identify patients who benefit from OFS.

Conflict of interest C. Dormann and K.J. Aichberger declare that they have no competing interests.

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