Editorial Commentary

More is not always better—what can be learned from the D-CARE trial

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Bone health is compromised in patients with breast cancer, which is mainly caused by treatment effects on bone density and/or quality. In particular, endocrine therapy, which is always given to hormone-receptor (HR) positive patients with early breast cancer for a long period of time—5 up to 10 years—impacts on bone health and may lead to increased fracture risk. According to the SOFT/TEXT trial the combination of GNRH agonist with aromatase inhibition is most effective to prevent disease recurrence in premenopausal HR positive patients at increased risk, but due to a drastic reduction in estrogen level this combination reduces bone mineral density (BMD) by more than 7% per year in those patients (1,2). In postmenopausal patients, aromatase inhibitors, which are the standard of care endocrine treatment, have been shown to reduce BMD and increase fracture risk (3).

Several prospective trials demonstrated that the preventive use of bisphosphonates or the anti-RANK-ligand antibody denosumab preserve bone health in those patients when given concomitantly with endocrine therapy. ABCSG-18, a phase III randomized placebo-controlled trial of 3,400 patients, showed that postmenopausal patients treated with AI have a high risk of clinical fractures up to 15% within 5 years, and that denosumab given at the dose of 60 mg s.c. every 6 months halves this fracture risk without any additional side effect, atypical fracture or osteonecrosis of the jaw (ONJ) (4). According to the body of evidence, bisphosphonates and denosumab, respectively, are recommended for patients with early HR positive breast cancer to preserve their bone health.

Beside those osteoprotective effects several early breast cancer trials have shown an impact of bisphosphonates on disease outcomes in patients with breast cancer. Direct antineoplastic effects of bisphosphonates have been described in experimental studies, but the major effect on disease progression in the clinic may be the immobilization of dormant cancer (stem) cells in the endosteal niche in the bone marrow. Breast cancer cells have been shown to undergo epithelial-mesenchymal transition (EMT), intravasate from their primary into circulation, undergo mesenchymal-epithelial transition (MET) and do their 'homing' in the bone marrow via several mechanisms like the expression of CXCR4 receptor expression (5). Within bone, these spread cancer cells can undergo dormancy and remain "silent" for years without forming overt metastases. Reactivation of those cells is triggered by several not fully described factors, which then lead to proliferation and development of (macro)metastases in the bone, and/or again intravasation leading to other distant metastases. Especially in HR positive breast cancer, this model is a valid explanation for the high frequency of bone metastases, but most importantly for the often very late development of distant metastases, sometimes many years after successful treatment of the primary in a putatively cancer-free patient.

Indeed, prospective trials showed an impact of the

adjuvant use of bisphosphonates on bone metastases and disease-free survival, however other trials were not able to show these effects. The EBCTCG meta-analysis demonstrated a significant improvement in bone recurrence and breast cancer mortality, but this positive effect on breast cancer outcome was restricted to postmenopausal women only (6). In line with that, a positive impact of adjuvant denosumab on breast cancer outcome was anticipated, but data were lacking.

Therefore, the rational consequence was the D-CARE trial by Coleman *et al.* with its aim to prove whether adjuvant denosumab can increase bone metastasis-free survival in patients with early breast cancer.

In this prospective placebo-controlled phase III trial, 4,509 patients with high-risk early breast cancer were randomized to receive neoadjuvant/adjuvant denosumab 120 mg subcutaneously every 3–4 weeks for 6 months and then every 12 weeks for up to 5 years versus placebo in combination with standard neoadjuvant/adjuvant treatment (7). The primary endpoint bone metastasis-free survival was a composite endpoint and included time to first bone metastasis irrespective of disease recurrence at other sites and death from any cause. The trial showed no significant difference between bone metastasis-free survival in patients treated with denosumab when compared to placebo. In the denosumab arm, 155 (7%) bone events and 137 (6%) deaths contributed to the composite primary endpoint versus 189 (8%) bone events and 116 (5%) deaths in the placebo arm. While disease-free survival also was not different between the groups, some bone-related exploratory end points showed positive signals (e.g., time to bone metastasis as site of first recurrence: D-Mab 110, Placebo 145, HR: 0.76). With respect to adverse events, 122 (5%) patients treated with denosumab developed ONJ versus 4 (<1%) patients in the placebo group. Atypical femur fracture occurred in 9 patients treated with denosumab versus no patient in the placebo group. No relevant difference in other adverse events was observed.

As a matter of fact, and as always in science, several important questions exist, and only a few have been definitively answered by this trial. Is the "negative" outcome of D-CARE trial mainly a result of the chosen suboptimal primary endpoint? Is it due to the study population (higher-risk EBC patients)? Was this trial underpowered to show any effect (probably not)? Was dosing and schedule of denosumab suboptimal in this trial? Is denosumab—in contrast to bisphosphonates—not able to impact on disease outcome?

The assumption that denosumab as a bone-targeted agent primarily impacts on bone metastases clearly led to the decision to choose bone metastasis-free survival as the primary endpoint. But, as this is a composite endpoint death from any cause is included and even though this was done in line with regulatory authorities, it may dilute the effect of denosumab on bone and even breast cancer outcomes, depending on the cause of death. This is of interest as more than 42% events of the primary endpoint were deaths from any cause in the D-CARE trial. One-third of deaths—and therefore nearly 15% of the primary endpoint events—were deaths without prior recurrence. According to the definition of the primary endpoint, all other deaths occurred before the development of bone metastases. Therefore, the addition of deaths to the primary endpoint clearly took away the focus on bone recurrence, but of course increased the number of events, and therefore seemingly the power of the trial.

It is well known that bone metastases occur most frequently in HR positive Her2 negative patients, irrespective of whether it is bone-only disease or bone metastases combined with other distant metastases (8). In triple negative breast cancer (TNBC), patients with bone metastases only are very rare (only about 4% of all metastatic patients), whereas more than 60% of TNBC patients develop distant visceral metastases without bone recurrence. Likewise, the development of bone metastases in Her2-positive disease is low.

About 65% of patients in D-CARE were HR positive and Her2 negative and therefore primarily contributing to a bone-targeted endpoint, resulting in 35% of patients who were contributing only little to the end point. Furthermore, all patients included in D-CARE were high-risk patients, meaning patients with a high risk to develop any distant metastases, but not in particular at high risk for bone metastases. Indeed, 428 (about 10%) of DFS events were non-bone distant recurrences, whereas only 255 (5–6%) events were bone metastases. If it is true that the main anti-tumor effect of denosumab is in the bone, the decision to choose a general high-risk population for the trial, intending to yield large number events—but not bone events in particular—in a short period of time may not have been be the right one.

Irrespective of the anti-tumor effect of denosumab, the incidence of a major adverse event, namely ONJ in the denosumab arm of D-CARE certainly is too high for any moderate benefit in terms of reducing bone recurrences as we know it from bisphosphonates. The incidence of ONJ is

below 1% with clodronate, ibandronate or zoledronic acid every 6 months (9-11). In the ABCSG-18 trial, in which patients received 60 mg denosumab subcutaneously every 6 months, no case of ONJ was observed with a median follow up of 73 months (4). The ONJ rate of patients treated with the more intense scheme of denosumab in D-CARE eventually was 5%. Such morbidity would require a huge benefit in terms of reducing bone recurrence to be accepted by the community, given that these patients, despite at higher overall recurrence risk, are early breast cancer patients of whom the majority can be considered cured.

In the EBCTCG bisphosphonates meta-analysis, no difference in efficacy between high-intensity and low-intensity treatment schemas could be detected (6). Reid *et al.* even reported prevention of fractures in osteopenic postmenopausal women with a de-escalated scheme of zoledronic acid (5 mg intravenously every 18 months) versus placebo (12). Additionally, they observed a reduction in the overall prevalence of cancers (OR: 0.67, CI: 0.50–0.89) with zoledronic acid, and no case of ONJ was observed. Of course, because of the different mechanisms of action between bisphosphonates, which stay in the bone for a long period of time, and denosumab, which acts more like an on-off switch of the RANK/RANK-L system, dosages and intensity of schemes and their impact on efficacy cannot be directly compared between these two antiresorptive bone-targeted agents. However, there is no indication whatsoever that a higher dose intensity by one or the other would improve its anti-cancer activity, but for sure a higher dose intensity increases adverse events. Coleman *et al.* conclude that '*the absence of beneficial effects on either disease free survival, breast cancer recurrence, or overall survival suggests that denosumab at the intensive dosing schedule selected for this study has no role in the management of early breast cancer*' (7). But is there really no role for denosumab in early breast cancer?

The AZURE trial, which investigated an intense scheme of zoledronic acid to improve disease-free survival in high-risk early breast cancer, concluded that the data '*do not support the routine use of zoledronic acid in the adjuvant management of breast cancer*' (13). Years and several analyses thereafter, bisphosphonates including zoledronic acid have been proven to impact on disease outcome in postmenopausal patients with early breast cancer, and therefore should be included in the treatment strategy in these patients, according to most of the available guidelines. Regarding denosumab, the analysis of the secondary endpoint disease-free survival of the ABCSG-18 trial, which investigated the impact of 60 mg denosumab subcutaneously every 6 months versus placebo on clinical fractures and outcomes, was positive (14). This trial included lower-risk postmenopausal patients with early HR positive breast cancer who were treated with an aromatase inhibitor. Denosumab significantly improved disease-free survival by an absolute difference of 3.1% after 8 years of follow up (HR: 0.82, log-rank P=0.0254). When looking at subgroups, there is no hint that patients at higher risk for relapse—node positive, T2–4, G3—derive more benefit compared to patients at lower risk, even though no definitive conclusion can be drawn. Interestingly enough, the biggest drivers for the difference in DFS are secondary primary invasive non-breast carcinoma, histologically verified (n=100, 5.9% in the placebo arm versus n=80, 4.7% in the denosumab arm). Thus, it might well be that denosumab inherits "general" anti-cancer activity that may not be restricted to effects in the bone alone. However, these thoughts are built on data from a secondary endpoint of a phase 3 trial, and therefore remain somewhat speculative.

Clearly, according to the D-CARE trial high-dose and intense application of denosumab for high-risk early breast cancer patients is not improving disease outcomes. However, some impact of denosumab on cancer is likely according to ABCSG-18 data. Therefore, the implementation of denosumab into a treatment strategy with the right dosing schedule for a clearly defined patient population appears possible in future. Until then, denosumab mainly remains a highly effective anti-resorptive agent, which prevents fractures in the osteoporotic population as well as in postmenopausal patients with HR positive early breast cancer treated with AI.

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Footnote

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Roche, and Medison. MG has served as a consultant for AstraZeneca and Eli-Lilly, and an immediate family member is employed by Sandoz.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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