Denosumab in the Treatment of Breast Cancer Patients with Bone Metastasis

Chair: Günther Steger

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Marth: The effects of denosumab on SRE in metastatic breast cancer were investigated in large randomized trials. Denosumab was superior to zolendronic acid in preventing SRE in patients with bone metastases from advanced cancer, regardless of ECOG performance status, number of bone metastases, presence/absence of baseline visceral metastasis, and urinary N-telopeptide (uNTx) level. Denusomab is therefore the first choice of treatment in breast cancer patients with bone metastases.

Question 2: In the Absence of Contraindications or Side Effects, How Long Do You Continue the Denosumab Treatment? Do You Change the Application Regimen (e.g. Frequency, Dose) after Prolonged Exposure to Denosumab (e.g. 2 Years) and If Yes, Do You Use a Standardized Protocol or Do You Decide on an Individual Basis? Are there Differences in Your Recommendations When Using Denosumab or Bisphosphonates?

Bartsch: This is a pertinent question as it was shown that the risk for osteonecrosis of the jaw (ONJ) increases with duration of bisphosphonate therapy [Bamias et al. J Clin Oncol 2005; 23: 8580–8858]. In general, in the absence of contraindications and relevant side-effects, I continue denosumab once every 4 weeks without any changes in the application regimen. In patients with stable bone metastases on zoledronic acid, extending the administration frequency from once every 4 weeks to once every 12 weeks appears to be reasonable, however, the ONJ rate was not reduced with this alternative regimen and uNTx concentration should be monitored [Amadori et al. Lancet Oncol 2013;14:663–670].

Fridrik: Denosumab can be administered by the patient herself and there is no need of creatinin monitoring before the application. Because of the convenience and the better tolerability we use denosumab for patients with bone metastases. However, the costs of the drug are more than 8 times higher than those of a biphosphonate.

Gampenrieder: Since denosumab has shown superiority in delaying skeletal related events (SRE) in breast cancer patients with bone metastasis and considering the lower rate of acute phase reactions as well as the more convenient subcutaneous administration, denosumab is our first choice for this indication. However, for patients with hypocalcemia at baseline or with a very low risk for a SRE, bisphosphonates are still an option.

Question 1: Is Denosumab in Combination with Standard Anti-Tumor Therapy Your Only ‘Gold Standard’ to Treat Advanced Breast Cancer Patients with Bone Metastasis or Is there Still a Role for Bisphosphonates in Your Daily Practice for this Indication?

Bartsch: A phase III clinical trial indicated superiority of denosumab as compared to zoledronic acid in terms of delaying or preventing skeletal-related events [Stopeck et al. J Clin Oncol 2010;28: 5132–5139]. Due to these results, denosumab is my drug of choice in patients with newly diagnosed bone metastases. In patients with stable disease still receiving antiresorptive therapy with bisphosphonates, however, I tend to continue this approach without switching treatment automatically to denosumab in the absence of progression or relevant side-effects.

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**Fridrik:** Denosumab is registered for 4-weekly dosing without an endpoint. Most studies applied denosumab until the first skeletal event. In a recent meta-analysis in *Annals of Oncology* the authors found no worsening of clinical outcome or bone-marker studies with de-escalation to 3-monthly applications. However, the side effects were similar. We use denosumab in the absence of hypercalcemia in 4-weekly intervals usually for 3 months and deescalate afterwards to 3-monthly intervals until the first skeletal event.

**Gampenrieder:** Since after suspension of denosumab a rebound effect of bone turnover occurs, leading to relatively rapid loss of bone mass, denosumab treatment is continued throughout palliative therapy. Also the application regimen remains unchanged. In contrast, based on the data of the OPTIMIZE-2 trial [Hortobagyi GN et al. ASCO 2014; abstr. LBA9500], the application frequency of zoledronic acid is generally reduced to 1 administration every 12 weeks after 1 year of treatment.

**Marth:** Bisphosphonates might accumulate in the bone and treatment duration should therefore be limited to approximately 3 years. For denosumab such a restriction in duration of treatment is not appropriate and we do not stop unless contraindications/toxicities occur.

**Question 3: Do You Use Standardized Procedures/Information Material to Inform Patients About the Risk for and the Prevention of Osteonecrosis of the Jaw (ONJ) before Starting the Denosumab Treatment and If Yes Which?**

**Bartsch:** Currently I do not use standardized material but individually inform every patient starting on antiresorptive therapy about the potential side effects and this naturally includes an extensive discussion of risk factors associated with ONJ as well as preventive measures. Furthermore, I routinely recommend an evaluation of the dental status before the initiation of denosumab.

**Fridrik:** In absence of hypercalcemia we start denosumab or bisphosphonates after examination by a dentist and dental treatment, if necessary. All patients receive written and verbal information.

**Gampenrieder:** No.

**Marth:** All patients are informed about ONJ and we recommend dental check-up in a timely manner.

**Question 4: How Do You Currently Treat Hypercalcemia?**

**Bartsch:** Malignant hypercalcemia is a potentially life-threatening complication of metastatic breast cancer. While severe hypercalcemia >3.5 mmol/l requires immediate and intense treatment, a less intense therapy may be used in patients with asymptomatic hypercalcemia ≤3.5 mmol/l. In patients with mild asymptomatic hypercalcemia, adequate hydration may suffice; in more severe cases, calcitonin and zoledronic acid are usually regarded as treatment standard. Further options consist of denosumab, administration of loop diuretics and hemodialysis in case of renal failure.

**Fridrik:** Hypercalcemic patients are dehydrated. Before any other treatment the patient has to be rehydrated. Mild hypercalcemia can be reversed by fluid replacement only. Patients with hormone sensitive disease, as breast cancer, prostate carcinoma, myeloma, or lymphoma, receive prednisolone. After fluid replacement we give zoledronic acid 8 mg i.v. in weekly intervals. Refractory hypercalcemia is treated with weekly denosumab for 4 applications and then every 4 weeks. In case of life-threatening hypercalcemia we use plasmapheresis and calcitonin.

**Gampenrieder:** Our standard treatment for malignant hypercalcemia is: i) hydration, ii) calcitonin 4 IE/kg s.c., iii) zoledronic acid 4 mg i.v.; denosumab is used in case of hypercalcemia refractory to zoledronic acid or if bisphosphonates are contraindicated due to severe renal impairment.

**Marth:** Treatment for hypercalcemia should be aimed both at lowering the serum calcium concentration and, if possible, treating the metastatic breast cancer. Effective treatments reduce serum calcium by inhibiting bone resorption, increasing urinary calcium excretion, or decreasing intestinal calcium absorption. In patients with moderate to severe hypercalcemia we start with volume expansion with isotonic saline adjusted to maintain the urine output at 100–150 ml/h. We typically combine denosumab and calcitonin in patients with calcium levels of >14 mg/dl who are also symptomatic. Since hypercalcemia is mostly associated with bone metastasis this is also the treatment of choice and after achieving normal calcium levels we continue with denosumab and cancer treatment.

**Question 5: Based on Published Data and the Current Prescription Label What Is Your Opinion About (and Practice for) the Adjuvant Use of Denosumab and What Kind of Further Studies/Data Would You Like to See in this Indication?**

**Bartsch:** In principle, the idea of using bisphosphonates and denosumab as additive treatment in the adjuvant setting is of great interest. The limiting factor, however, is the fact that these drugs are currently not licensed for the use in the adjuvant setting in the absence of osteoporosis. Still, ABCSG-18 clearly indicated that independent of baseline bone mineral density, denosumab reduced fracture rates in breast cancer patients on adjuvant endocrine therapy to a clinically meaningful extent [Gnant et al. Lancet 2015;386: 433–443]. On the other hand, bisphosphonates reduced breast cancer recurrences and improved survival as shown in a recent EBCTCG meta-analysis [EBCTCG. Lancet 2015;386:1353–1361].
A similar – albeit non-significant – trend in favor of denosumab was observed in ABCSG-18. To resolve this dilemma in daily clinical practice, I tend to initiate anti-resorptive treatment as early as possible in patients receiving adjuvant endocrine therapy when a reduction of bone-mineral density is observed or the patient is believed to be at an increased fracture risk. With regard to clinical studies, results of the D-CARE trial (NCT01077154) evaluating the effect of denosumab on disease recurrence as primary endpoint are eagerly awaited.

**Fridrik:** In ABCSG-18 patients without osteoporosis and adjuvant treatment with an aromatase inhibitor the rate of clinical bone fractures could be reduced to 50% by denosumab 60 mg every 6 months. We recommend denosumab for the prevention of bone fractures in patients treated with aromatase inhibitors according to ABCSG-18. We urgently need a label for this indication. We are eagerly waiting for the long-term results of the secondary tumor endpoints of ABCSG-18.

**Gampenrieder:** Our standard adjuvant bone therapy for ER-positive early breast cancer remains zoledronic acid 4 mg every 6 months due to the survival benefit with adjuvant bisphosphonates shown in the meta-analysis. Denosumab is used in case of acute-phase reactions after zoledronic acid administration or other side effects. Data from the D-CARE trial are awaited and a meta-analysis of ABCSG-18 and D-CARE would be appreciated to see if a survival benefit can be achieved by denosumab as well.

**Marth:** Based on the results of our ABCSG-18 trial we recommend a combination of anastrozole and denosumab for postmenopausal HR-positive early breast cancer patients according the inclusion criteria. Further confirming trials are, however, needed.