Incidence of hypocalcemia in metastatic breast cancer patients under treatment with denosumab: A non-inferiority phase III trial assessing prevention of symptomatic skeletal events (SSE) with denosumab administered every 4 weeks versus every 12 weeks


Kantonsspital Winterthur, Winterthur, CH, *St. Claraspital, Basel, CH, †SAKK Coordinating Center, Bern, CH, ‡Kantonsspital St. Gallen, St. Gallen, CH, §Kantonsspital Graubünden, Chur, CH, ‡University Hospital Zürich, Zürich, CH, ¶OISI, Bellinzona, CH, ‡Kantonsspital Baden, Baden, CH, †Kantonsspital Aarau, Aarau, CH, #Spital STAS AG, Thun, CH, §Spital Thurgau, Münsterlingen, CH, ¶HFR Freiburg - Kantonsspital, Freiburg, CH, ¶CHUV, Lausanne, CH, ¶HUG, Geneva, CH, †Hirslanden Clinic Aarau, Aarau, CH, ¶University Hospital Basel, Basel, CH, ¶Klininpait, Bern, CH, ¶Engelbert & Lindenhofer, Bern, CH

Background

• Bone metastases are a major burden in patients with advanced breast cancer [BC] and may lead to skeletal related events [SRE]. Denosumab is a human monoclonal antibody against RANKL (Receptor Activator of Nuclear Factor kappa-B Ligand) which is involved in the modulation of osteoclast activity and bone resorption. It is given subcutaneously on a weekly or every 4 weeks [q4w] basis. Despite its use in indications such as osteoporosis in postmenopausal women or treatment of bone metastases in patients with advanced prostate cancer, there is no experience with denosumab in the treatment of skeletal complications in BC patients.

• Denosumab [DN] (a monoclonal antibody against RANK-Ligand) has been shown to be superior to ZA in delaying time to first SRE in patients with bone metastases from BC [1].

• Newer data have shown that ZA given every 12 weeks [q12w] is non-inferior to ZA given every 4 weeks [q4w] [2].

• This rate is considerably higher than the numbers reported in the registration trials of DN (where it was 5.5% for breast cancer [2]).

• Denosumab given every 12 weeks as induction treatment after 4 weeks of induction [q12w] was associated with a non-inferiority phase III trial assessing prevention of symptomatic skeletal events (SSE) [3].

• This suggests that DN given q12w has a more favorable long term safety profile in terms of SSE compared to DN q4w.

Results

• This safety-interaction analysis was performed after 3.5 years of accrual with N=351 BC patients.

• HC was the most common side effect with a rate of 24.8% in Arm A (q4w) whereas it worsened in more patients in Arm A than in Arm B (table 1), thus a remarkable difference for HC resulted for the two arms after 1 year.

• After 1 year of treatment, the rate of HC compared to the induction phase had decreased in Arm B but not in Arm A (24.8% vs. 12.1%).

• Grade 3 HC was observed in 0.3%, no grade 4 HC occurred (table 2).

• Treatment associated hypocalcemia occurs early and is rare after > 64 weeks (figure 2).

Methods

• Patients with at least 3 bone metastases from BC (or castration resistant prostate cancer [CRPC]) not reported to skeletal related events [SRE]. Denosumab was administered as 120 mg SC q4w or q12w.

• After induction phase DN q4w was continued in Arm A whereas it worsened in more patients in Arm A than in Arm B (table 1). There was no statistical difference in bone specific pretreatment for bone metastases was randomised: 1: 1 Arm A ( Arm A q4w; Arm B q12w) whereas it worsened in more patients in Arm A than in Arm B (table 1) and a true difference in bone specific pretreatment for bone metastases was randomised: 1: 1 Arm A ( Arm A q4w; Arm B q12w) whereas it worsened in more patients in Arm A than in Arm B (table 1).

• This rate is considerably higher than the numbers reported in the registration trials of DN (where it was 5.5% for breast cancer [2]).

• Denosumab given every 12 weeks as induction treatment after 4 weeks of induction [q12w] was associated with a non-inferiority phase III trial assessing prevention of symptomatic skeletal events (SSE) [3].

• This suggests that DN given q12w has a more favorable long term safety profile in terms of SSE compared to DN q4w.

Conclusions

• Up to 20% of all BC patients with metastatic disease [2] experienced hypocalcemia [HC] in the q4w induction phase despite mandatory supplementation of VitD and Ca and measurement of Ca before each injection.

• This rate is considerably higher than the numbers reported in the registration trials of DN (where it was 5.5% for breast cancer [2]).

• After the induction phase, HC is markedly reduced in the q12w arm compared to the q4w arm.

• This suggests that DN given q12w has a more favorable long-term safety profile in terms of HC compared to DN q4w.

References


Acknowledgements

We thank the Swiss State Secretariat for Education, Research and Innovation (SERI) and the Swiss Health insurance companies associated with santéssuisse for supporting this trial.

Figure 1: Hypocalcemia by grade and treatment arm (BC cohort)

Table 1: Change in HC grade after week 16* in patients with BC during induction treatment (N=581) in both cohorts

| Arm | Baseline | Week 16 | Δ (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>B</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Δ: Decrease from baseline; Week 16: i.e. the time when the schedules of DN begin to differ between Arm A and Arm B.

Table 2: Hypocalcemia by grade and treatment arm (BC cohort)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition according to CTCAE 4.0</th>
<th>Arm A q4w</th>
<th>Arm B q12w</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>273 (38%)</td>
<td>122 (25%)</td>
<td>197 (21%)</td>
<td>0.017</td>
</tr>
<tr>
<td>1</td>
<td>51 (7%)</td>
<td>9 (2%)</td>
<td>42 (5%)</td>
<td>0.008</td>
</tr>
<tr>
<td>2</td>
<td>1 (0.1%)</td>
<td>0 (0%)</td>
<td>1 (0.1%)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*Δ: Decrease from baseline; Week 16: i.e. the time when the schedules of DN begin to differ between Arm A and Arm B.