Bone healing in multiple myeloma: A prospective evaluation of the impact of first-line anti-myeloma treatment

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Bone healing in multiple myeloma: A prospective evaluation of the impact of first-line anti-myeloma treatment

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Running title: Bone healing in multiple myeloma

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Acknowledgments
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This study was supported by funding from Janssen. A study grant was awarded to MH from the University of Southern Denmark; Lillebaelt Hospital, Denmark; and The Danish Cancer Society.

Key words: Multiple myeloma, bone disease, osteolytic lesion, bone marker, bone sclerosis
Myeloma cells disturb a normally balanced bone remodeling process. This imbalance of bone metabolism may cause osteopenic bones, focal osteolytic lesions and clinical symptoms. The excess bone resorption resulting in osteolytic lesions has traditionally been perceived as irreversible. We investigated the potential for bone healing in a prospective study of previously untreated multiple myeloma (MM) patients using a five-drug bortezomib-containing treatment regimen. Using low-dose computed tomography (CT) we observed that 68% of the osteolytic lesions developed an osteosclerotic rim perceived as an early sign of healing, while 14% of the lesions showed a reduction in size during treatment and up to 18 months of follow-up.

Thirty-five newly diagnosed MM patients requiring treatment were enrolled in a prospective single centre phase-II study, to evaluate the safety and efficacy of first-line treatment with a five-drug combination (ACVDL). This clinical trial was approved by The Regional Scientific Ethical Committees for Southern Denmark and registered at ClinicalTrials.gov (NCT01481194). EUDRACT number 2011-002751-34. All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice.

As a secondary end point to this clinical trial, the impact of ACVDL on bone involvement in MM was evaluated in patients who completed three or more consecutive bone examinations at pre-specified time points. Bone status was evaluated using low-dose CT-scan, bone single photo emission computed tomography (SPECT)/CT-scan and serum markers of bone turnover at baseline, after four cycles of ACVDL (12 weeks), at end of treatment assessment (EoT) (approximately 28 weeks) and thereafter every six months.

Well-defined osteolytic lesions with a diameter of ≥10 mm on CT-scans were identified as target lesions at baseline. Each target lesion was then evaluated in terms of size and development of osteosclerosis in all consecutive CT-scans. The presence of osteosclerosis at the edge of a target lesion was interpreted as an early sign of healing and classified dichotomously either as being present or not present (Figure 1). More pronounced formation of sclerotic bone, together with a simultaneous reduction in the largest diameter of the osteolytic lesion by ≥30%, was interpreted as a more advanced sign of healing (Figure 1). Tracer uptake by the osteolytic target lesions by bone SPECT was classified either as decreased, equal to or increased when compared to uninvolved bone.
The serum bone resorption marker C-terminal telopeptide type-I (CTX) and the serum bone formation marker N-terminal propeptide of procollagen I (P1NP) were measured in fasting blood samples collected in the morning.

Twenty-eight of the 35 enrolled patients completed three or more consecutive bone examinations. Among these, 18 patients showed at least one osteolytic lesion that qualified as a target lesion. (Supplementary table 1).

Fifty-six osteolytic target lesions in 18 patients were followed over time, 34% of which had increased tracer uptake at the baseline bone-SPECT.

Sclerosis appeared in 68% of all target lesions. In 63% of these lesions, sclerosis had already appeared at the interim CT-scan (12 weeks after initiation of treatment). In 24% sclerosis appeared at the EoT CT-scan (28 weeks after initiation of treatment), while in the remaining 13% of lesions sclerosis appeared during the follow-up period. Healing (size reduction) was seen in 14% of the osteolytic target lesions (Figure 2).

Sclerosis appeared at different hematological responses; 58% with complete remission (CR) or very good partial remission (VGPR), and 24% at partial response (PR) and 18% at less. Increased baseline bone SPECT uptake had a tendency to be associated with development of sclerosis (p=0.08).

Of the patients with osteolytic target lesions, 72% had at least one lesion with development of sclerosis, while 56% had target lesions both with development of sclerosis and lesions with no response. Thirty-nine percent of the patients with osteolytic target lesions had at least one lesion with healing (size reduction)(supplementary table 2).

The serum level of the bone formation marker P1NP showed a significant decrease from baseline to interim (p<0.01), before P1NP levels increased from interim to EoT (p<0.001) (Figure 3A). Serum P1NP levels were significantly higher at EoT than at any other time points.

The serum levels of the bone resorption marker CTX was higher at baseline compared with any subsequent measurement in the majority of patients (Figure 3B).

In recent years, the introduction of several novel agents for treatment of MM has improved survival. In order to improve quality of life it is also important to control the bone lesions and if possible revert bone damage that has already occurred.

In addressing the impact of a 5-drug bortezomib-containing treatment on bone healing in MM, we found development of a rim of sclerosis in the osteolytic lesions of the majority of the patients and
that some osteolytic lesions also showed more profound signs of healing. While sclerosis was observed in all the lesions from a small number of patients, a heterogeneous response was found in individual patients in general, with some lesions showing sclerosis or healing and some showing no response.

We found that 72% of the patients with osteolytic target lesions developed bone sclerosis. This is far greater than the 18% reported from a retrospective study of MM patients receiving various bortezomib-containing regimens when also taking into account that the study of Schulze et al included patients without osteolytic lesions. The discrepancy may be due to the fact that only 14% of the patients in the study by Schulze et al received first-line treatment. It is likely that osteolytic lesions that have existed for a long time may lose their potential for healing. Furthermore, osteolytic lesions with a minimum size of 10 mm were only considered. Whether the size of a lesion plays a role in its healing potential is less certain.

We found that signs of sclerosis and healing were seen in all levels of responses to anti-myeloma treatment, as previously reported. Bone sclerosis often appeared before the best hematological response was achieved. In some patients sclerosis or healing was seen during follow-up, indicating improved bone metabolism during the period of remission.

Increased tracer uptake by bone SPECT was more frequently seen, but not significant, in lesions that developed osteosclerosis. This observation suggests that the healing potential of an osteolytic lesion may be dependent on the degree of perturbation of the microenvironment at the time of treatment initiation. Andersen et al. have shown that myeloma cells disrupt a micro-anatomical structure; the bone remodeling compartment that appears to be of crucial importance for maintaining the integrity of bone. The extent of local disruption of the bone remodeling compartments may influence the capacity to initiate new bone formation at a later point in time. The suggested correlation between increased baseline bone SPECT activity and subsequent formation of sclerosis in osteolytic lesions supports the assumption that if the capacity to form new bone locally has been totally eliminated the chance of recovery is poor.

We found an increase of the bone formation marker P1NP during treatment with a peak at the EoT where the patients had obtained the maximum response to anti-myeloma treatment. The bone formation at this point in time may compensate for the increased bone loss that occurred at the time of diagnosis. Even though we were unable to determine to what extent the increased bone formation was driven by a specific component of the therapy (bortezomib), the result did show that treatment can improve bone formation in MM as previously reported. CTX, the serum marker of bone
resorption, dropped rapidly following initiation of anti-myeloma treatment, which was in agreement with previous studies.\textsuperscript{8,9} In our study, serum CTX levels remained suppressed following initiation of anti-myeloma treatment, with the inclusion of zoledronate for the majority of patients. Decreased values of bone resorption markers were recently reported in MM patients receiving VTD (bortezomib, thalidomide, dexamethasone) consolidation after autologous stem cell transplantation, but without bisphosphonate treatment.\textsuperscript{10} This observation supports the view that effective treatment of MM itself is a key factor in the control of excessive bone resorption. Thus, it is reasonable to suggest that both anti-myeloma treatment and bisphosphonates play a role in the control of excessive bone resorption in MM. The combination of specific drugs used to treat myeloma may have significance for the effect on bone, since bortezomib has previously been reported to increase bone formation evaluated by serum bone markers in responding patients,\textsuperscript{11,12} unlike lenalidomide, which had no influence on the effect\textsuperscript{8}. The present trial included both bortezomib and lenalidomide in a combined treatment (supplementary methods) as an attempt to optimize disease control. This prospective study showed that osteolytic lesions may, at the very least, be partially reversible in the majority of responding patients. Nevertheless, our data also showed intra-patient variation with respect to re-induction of bone formation in the osteolytic lesions. As a consequence, the degree of destruction of the microenvironment within the individual osteolytic lesion may have implications for any possibility of achieving healing of the lesion.

**Acknowledgments**

The authors would like to thank the study nurses at the Clinical Research Unit of Hematology, Vejle Hospital for their work regarding the ACVDL-protocol.

**Funding**

This study was supported by funding from Janssen. A study grant was awarded to MH from the University of Southern Denmark; Lillebaelt Hospital, Denmark; and The Danish Cancer Society.
Reference List


Figure legends:

Figure 1:
Title: Sclerosis and healing
Illustration of an osteolytic lesion with development of sclerosis and another lesion with development of both sclerosis and size-reduction.

Figure 2:
Title: Sclerosis and healing of osteolytic target lesions.
Time for development of sclerosis or healing of the 56 osteolytic target lesions observed in 18 patients. The number refers to the patient id and each patient have between 1 and 5 target lesions. The circles illustrate the target lesions and the color of the circles illustrated the status at different time points. Each row shows different time points from baseline to interim assessment, end of treatment and follow-up. Boxes without circles indicate missing scans. Note the variability of responses in individual patients.

Figure 3:
Title: Effect of treatment on serum markers of bone turnover during treatment and follow-up.
A: The level of the bone formation marker N-terminal propeptide of procollagen I (P1NP), decreased from baseline to interim and then increased to the highest level at end of treatment. After treatment completion a decrease was seen.
B: The highest level of the bone resorption marker C-terminal telopeptide (CTX) was seen at baseline with a rapid drop after initiation of treatment. None of the three patients with sustained high serum levels of CTX received treatment with bisphosphonates.
EoT: End of treatment; FU1, 2 and 3: follow-up assessments 6, 12 and 18 months after end of treatment.
* = p<0.05, ** = p<0.01, *** = p<0.001.
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○ Osteolytic target lesion with no response
○● Osteolytic target lesion with development of sclerosis
● Osteolytic target lesion with healing
Supplementary material

Supplementary methods

Patients

Thirty-five patients above 18 years with newly diagnosed MM in need of treatment according to the CRAB criteria were enrolled in a prospective single centre phase-II study, evaluating the safety and efficacy of first-line treatment with a five-drug combination (ACVDL) given in 21 day cycles: Doxorubicin, 50 mg/m² iv on day 1; Cyclophosphamide, 750 mg/m² iv on day 1; Bortezomib, 1.3 mg/m² iv on day 2 and 9; Dexamethasone, 20 mg orally on day 2, 3, 9 and 10. Lenalidomide 15 mg orally from day 1 to 14.

Patients eligible for autologous stem cell transplantation (ASCT) received four cycles of ACVDL followed by ASCT, while patients ineligible for ASCT received eight cycles of ACVDL. Five 5-week cycles of consolidation therapy with subcutaneous bortezomib (1.6 mg/m² sc, day 1, 8, 15, 22) were offered to patients who were not in complete molecular remission (mCR) on completion of ACVDL treatment (EoT).

The clinical trial was approved by The Regional Scientific Ethical Committees for Southern Denmark (id: 2011-0123) and registered at ClinicalTrials.gov (NCT01481194) and by EUDRACT number 2011-002751-34. Written informed consent was provided by all patients in the study. The study was conducted in accordance to the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice.

A secondary end point of this clinical study was to evaluate the impact of the study treatment on bone involvement in MM.

Bone assessments

Bone status was evaluated using low-dose computed tomography (CT) scan, bone single photon emission computed tomography CT-scan (bone SPECT/CT) and serum markers of bone turnover. Bone examinations were performed at baseline, after four cycles of ACVDL, at EoT (three months after ASCT or four weeks after completing eight cycles of ACVDL) and thereafter every six months until patient withdrawal from the study or completion of the trial.

Hematological response to the ACVDL treatment was evaluated according to the International Myeloma Working Group Uniform Response Criteria simultaneously with the CT-scans.

All examinations were performed at Vejle Hospital, Denmark in the period from November 2011 until a data cut-off point on 2nd July 2015.
**Low-dose CT**

CT-examinations were conducted as low-dose scans (120 KV, 70 mAs reference with dose modulation) without use of contrast medium and with a reconstruction slice thickness of 3 mm on the bone algorithm. Low-dose CT imaging was obtained using either Philips Gemini TF 16 slices or Philips Gemini TF 64 slices equipment and, on a small number of occasions, in combination with bone SPECT-scans at a 16 slice Philips Percedence. Patients were scanned from the skull to below the knees. Images were assessed by experienced radiologists. CT-scans performed at the time of MM relapse or progression were also included in the study.

**Bone SPECT/CT**

Bone SPECT/CT was performed to investigate if the osteolytic lesions would increase their tracer uptake after anti-myeloma treatment as a sign of increased osteoblastic activity. Three hours prior to bone SPECT/CT acquisition, patients were injected with 700 MBq of tracer 99m-Tc-HDP (hydroxy-methylen-difosfonate) (Technescan HDP®, Mallinckrodt, Switzerland). This labeled bisphosphonate tracer is taken up at sites where mineral deposition occurs and therefore bone SPECT-uptake can be considered a surrogate marker for the activity of bone forming osteoblasts. The equipment employed was a 16 slices Philips Precedence. Bone SPECT scan was reconstructed with CT attenuation correction (140 KV, 50 mAs reference with dose modulation) and resolution recovery (Astonish®). Bone SPECT covered either one or two fields of view of the axial skeleton, with the most osteolytic lesions seen on the CT. Images were evaluated by experienced nuclear medicine physicians.

**Osteolytic target lesions by CT and bone SPECT/CT**

Well-defined osteolytic lesions with a diameter of ≥10 mm on CT-scans were identified as target lesions at the baseline. Up to five target lesions were identified from each patient. Each target lesion was then evaluated in terms of size and development of osteosclerosis (visual increase in density from the baseline) in all consecutive CT scans. The presence of osteosclerosis at the edge of a target lesion was interpreted as an early sign of healing and was classified dichotomously as being either present or not present. More extensive formation of sclerotic bone, together with a simultaneous reduction of the largest diameter of the osteolytic lesion by more than 30%, was interpreted as an advanced sign of healing of the target lesion (Figure 1). A reduction in size of an osteolytic lesion by ≥30 % was defined as significant for bone healing. This was adapted from the Response...
Evaluation Criteria in Solid Tumours (RECIST)\textsuperscript{4} since no standard scoring system for healing of osteolytic lesions in MM is available.

Tracer uptake by the osteolytic target lesions was classified either as decreased, equal to or increased when compared to the surrounding uninvolved bone on the bone SPECT.

**Serum markers of bone turnover**

Fasting blood samples were collected for measurement of the bone resorption marker C-terminal telopeptide type-I (CTX) (β-CrossLaps, Roche Diagnostics) and the bone formation marker N-terminal propeptide of procollagen I (P1NP) (Total P1NP, Roche Diagnostics). Samples collected at the time of relapse or progressive MM were excluded from the calculations, since the serum levels of these markers have been shown to change rapidly in cases of MM relapse.\textsuperscript{5}

**Statistics**

The mixed model with random slope clustered for individuals was used to analyze repeated measurements of the serum marker of bone turnover. Calculations were performed using Stata 12 software.

Reduction in the size of osteolytic lesions was expressed as percentage of the largest baseline diameter. Fisher’s exact test was used to calculate the difference in bone SPECT tracer uptake between osteolytic lesions with and without healing or development of sclerosis. Calculations were performed using Graph Pad Prism software. A two-sided p-value <0.05 was considered statistically significant.
Reference List


Patient characteristics

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Patient characteristics of the cohort of 28 patients sequentially followed with serum markers of bone turnover and the 18 patients with osteolytic target lesions followed by computer tomography and bone single photon emission tomography. ISS: international staging system; ASCT: autologous stem cell transplantation; SD: stable disease; PR: partial remission; VGPR: very good partial remission; ≥CR: complete response including stringent CR and molecular CR, ACVDL: treatment with doxorubicin, cyclophosphamide, bortezomib, dexamethasone and lenalidomide.
### Supplementary table; S2

**Ostelytic lesions with healing**

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<td>35 x 13</td>
<td>VGPR</td>
<td></td>
</tr>
</tbody>
</table>

Healing was defined as a size reduction of $\geq 30\%$. Target lesions no. 7 and 8 are from the same patient. The colored squares in the first column serve to identify the diagram of individual patient’s levels of the bone formation marker P1NP shown on the right hand side. The colored squares in the graphs of the serum P1NP-levels illustrate the time where healing was first observed by low-dose CT-scan.

OTL: osteolytic target lesion; MM: multiple myeloma; EoT: end of treatment; FU1: first follow-up at 6 months; FU2: second follow-up at 12 months; SD: stable disease; PR: partial remission; VGPR: very good partial remission; CR: complete response. P1NP; N-terminal propeptide of procollagen I.