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

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Supplementary material

Supplementary methods

Patients

Thirty-five patients above 18 years with newly diagnosed MM in need of treatment according to the CRAB criteria[1] 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/m^2 iv on day 1; Cyclophosphamide, 750 mg/m^2 iv on day 1; Bortezomib, 1.3 mg/m^2 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.[2] 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/m^2 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[3] 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)[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.[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

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Supplementary table; S1

Patient characteristics

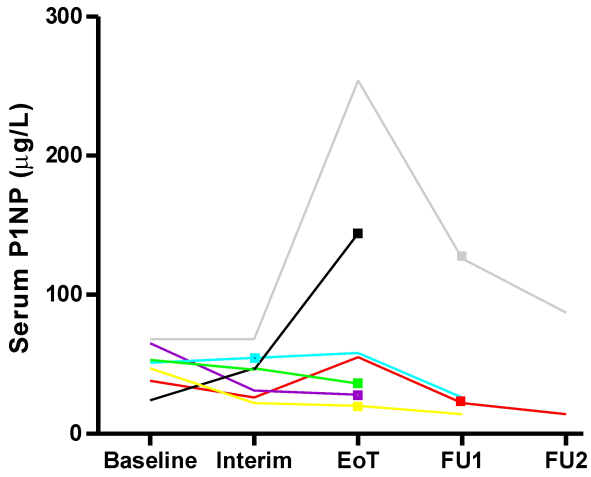
Patient characteristics	Bone marker n:28	Osteolytic Target lesions n:18
Mean age:	63 (49-81)	62 (49-71)
Sex:		
Male	57 %	56 %
Female	43 %	44 %
ISS:		
1	46 %	44 %
2	39 %	33 %
3	14 %	22 %
ASCT:		
Yes	61 %	67 %
No	39 %	33 %
Consolidation therapy:		
Yes	64 %	61 %
No	36 %	39 %
Best treatment-response:		
SD	4 %	6 %
PR	29 %	22 %
VGPR	21 %	33 %
≥ CR	46 %	39 %
Zoledronate treatment:		
Yes	75 %	83 %
No	25 %	17 %
Anti-resorptive treatment before ACVDL:		
Yes	14 %	11 %
No	86 %	89 %

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 doxorubincin, cyclophophamide, bortezomib, dexamethasone and lenalidomide.

Supplementary table; S2

Ostelytic lesions with healing

OTL No.	Sex/ Age	OTL location	OTL size at baseline (mm)	MM status at the time of healing	P1NP and Time for healing of OTL
1 ■	F/56	Th6	28 x 16	SD	
2 ■	F/69	Scapula	11 X 6	CR	
3 ■	F/51	Costa 5	45 x 22	CR	
4 ■	F/69	Costa 9	13 x 6	PR	
5 ■	M/57	Costa 5	38 x 19	PR	
6 ■	M/71	Scapula	14 x 12	CR	
7 ■	F/61	Skull	16 x 8	VGPR	
8 ■	F/61	Os Ilium	35 x 13	VGPR	



Healing was defined as a size reduction of ≥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.