Physical function in patients with newly diagnosed multiple myeloma given monthly infusions of 30 mg versus 90 mg pamidronate: results of a randomized blinded Nordic Myeloma Study Group (NMSG) trial.

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Abstract

Background: Prophylactic treatment with bisphosphonates reduces skeletal events in multiple myeloma compared with placebo. However, the toxicity associated with long-term treatment makes it important to find the lowest effective dose. The aim of this study was to compare the effect of two doses of pamidronate on health- related quality of life and skeletal morbidity in patients with newly diagnosed multjple myeloma.

Methods: Multiple myeloma patients starting antimyeloma treatment were randomly assigned to monthly infusions of 30 mg (P30) or 90 mg (P90) pamidronate for at least 3 years in a blinded design. Patients were followed every third month for quality of life, skeletal-related events (SRE) and response. Primary outcome was physical function after 12 months assessed by the EORTC QLQ-C30 questionnaire. This study is registered with ClinicalTrials.gov, number NCT00376883.

Findings: From January 2001 until August 2005, 252 patients were randomly assigned to P30 and 252 to P90. Physical function at 12 months showed no significant difference (mean score: P90: 66; P30: 68; CI of difference -6.6 to 3.3, p=0.52). Other QLQ variables like pain, fatigue and global health scores showed no significant difference between the two groups (at 12 months, pain score, p= 0.33; fatigue, p= 0.22; global health score, p=0.23; similar results throughout the whole period). There was no significant difference of time to first SRE between P90 and P30 (p=0.48) or for surviving without skeletal event (p=0.51).

Interpretations: Monthly infusion of 90 mg pamidronate is not more effective than 30 mg in newly diagnosed myeloma patients. Thus pamidronate 30 mg can be the recommended dose to prevent bone disease in multiple myeloma.*Funding:* Nordic Cance Union, Novartis Denmark

Introduction

In multiple myeloma, a malignant plasma cell disorder, bone involvement has major implications for morbidity during the course of the disease. Malignant plasma cells stimulate the recruitment and activity of osteoclasts directly and indirectly through various cytokine pathways involving RANKL and RANK, and simultaneously inhibit the osteoblasts(1). The result is progressive osteolytic bone lesions with bone pain, pathologic fractures and hypercalcemia, which all have a major impact on quality of life.

Bisphosphonates inhibit recruitment and activity of osteoclasts and have been used for prophylactic treatment of bone disease in multiple myeloma and in other malignant diseases with bone metastases. Early randomized placebo-controlled trials showed significant effects of oral clodronate(2;3) and intravenous pamidronate(4;5) on the bone disease. Later, the more potent zoledronic acid showed equivalent effect compared with pamidronate in multiple myeloma(6). When comparing the antiresorptive effect the bisphosphonate dose-intensity has increased considerably from clodronate through pamidronate to zoledronic acid. Recently the Medical Research Council Myeloma IX Trial showed improved effect of zoledronic acid compared to clodronate on both skeletal related event and overall survival(7). However, the dose for maximal prophylactic effect is not known. While most trials have focused on skeletal events, few data have been published on prospective evaluation of the quality of life.

The myeloma treatment itself has an important effect on the bone disease showing increasing bone density in patients responding to conventional chemotherapy(8). The combination of high-dose melphalan (HDM) with autologous stem cell support (ASCT) and bisphosphonate treatment has

furthermore showed that the dysregulation of RANKL, RANK(9), and the Dickkopf-1 protein(10) is normalized.

Laboratory studies have shown a direct and dose-dependent anti-myeloma effect of bisphosphonates in cell-lines(11) while the in vivo effect is less well documented(12;13). Attempts to use higher doses of pamidronate and zoledronic acid had to be stopped due to an increased risk of renal impairment e.g. the development of glomerulosclerosis after pamidronate treatment (14). It has recently been shown that long-term treatment with pamidronate and zoledronate seems to increase the risk of developing osteonecrosis of the jaw (BON)(15). Due to increased awareness of long term toxicity of bisphosphonates, it has recently been recommended to restrict the time on treatment to two years(16). Furthermore, to avoid toxicity it seems important to explore the lowest effective dose of bisphosphonates.

The objectives of the trial is to compare, in a randomized, blinded clinical trial, the effect of two doses of intravenous pamidronate (Novartis Pharmaceuticals Corporation, New Jersey, US) (30 mg (P30) versus 90 mg (P90)) in previously untreated patients with multiple myeloma. As the ultimate aim of bisphosphonate therapy is to improve quality of life, patient-reported physical function as determined by the EORTC quality of life questionnaire, the QLQ-C30, was chosen as the primary outcome measure. Skeletal events were analyzed as a secondary outcome measure, and though not pre-planned the trial also allowed us to evaluate retrospectively the occurrence of BON.

Methods

Patients

The trial population consists of patients with untreated symptomatic multiple myeloma presenting at 37 clinics in Denmark, Norway and Sweden from January 2001 until August 2005. Study medication was initiated within the first month of anti-myeloma therapy. Patients not eligible for high-dose therapy were given melphalan and prednisone (MP) with or without thalidomide. Patients aiming at HDM and ASCT received VAD (vincristine, adriamycin, dexamethasone) or CyDex (cyclophosphamide, dexamethasone)(17) as induction therapy. Exclusion criteria were P-creatinine above 400 µmol/l, expected survival less than three months, and previous treatment with bisphosphonates for more than two of the last six months.

Intervention, randomization and blinding

Patients were centrally allocated to receive 30 mg (P30) or 90 mg (P90) pamidronate (Aredia®) as intravenous infusion for 2½ hours every month, administered as double-blind doses. The clinical investigators called The Copenhagen Trial Unit and informed about patient data and stratification variables. The Copenhagen Trial Unit then conducted the central randomization and send the information to the drug distributor, Amgros I/S, Copenhagen. The centralized randomization used a computerized minimization system developed according to Pocock (18). In case the system required random allocation, then we used computerized randomization based on a computer generated allocation sequence without blocking, which randomised participants 1:1 to experimental and control intervention. We stratified the participants according to country (Sweden or not Sweden), pre-planned HDM and ASCT or not, beta-2 microglobulin level (< 2.6 mg/l, ≥ 2.6 mg/l or performance status (WHO ≤ 2 or > 2 and whether or not the patient was included in another Nordic myelomatosis trial (MP with or without thalidomide). The allocation ratio was 1:1. The drug distributor mailed the allocated dose for the specified patient to a local pharmacy, which was responsible for preparing the blinded infusion bag for the clinic. In clinics at smaller hospitals without a local pharmacy an entrusted person was responsible

for the blinding. The patients and their doctor were kept unaware of the allocated dose. The treatment was continued for at least 3 years, with the option that patients could continue treatment further. After final approval of the collected data the statistician was informed of the allocation groups. After statistical analysis was performed Copenhagen Trial Unit unblinded the actual dose of the two groups.

The trial was conducted according to the Declaration of Helsinki after written informed consent, and was approved by the ethical committees and health authorities in Denmark, Norway and Sweden. The data were monitored by the regional coordinators of NMSG.

When 200 patients had been followed for 6 months from inclusion the independent Monitoring and Safety Committee conducted an interim analysis for toxicity and concluded that the trial could continue.

Assessments

Quality of life was evaluated by the EORTC QLQ-C30(18). Questionnaires were handed to the patients at inclusion and subsequently mailed directly to the patient every third month.

The patients were followed every third month for disease status, skeletal events, height, toxicity including creatinine and calcium. Skeletal events were defined as spontaneous fracture, new vertebral compression, new osteolytic lesions demanding irradiation therapy or surgery(4), symptomatic progression of known osteolytic lesions or hypercalcemia(19). Skeletal survey was to be performed at baseline and after 9 and 24 months. The local radiological departments reported their evaluation: Progression was defined by a 25% progression of existing osteolytic lesions or vertebral fractures, or by development of new osteolytic lesions or fractures. Regression was defined by a >25% reduction in size of lesions or by healing. All obtainable radiographs were collected, and centrally reviewed blinded for

intervention by one experienced radiologist in order to calculate arbitrary X-ray scores; a total osteolysis score, an osteoporosis score, a vertebral fracture score, and a non-vertebral fracture score. Each region (calvarium, cervical, thoracic and lumbar spines, pelvis, thorax, and long bones of arms and legs) was scored for number and size of osteolytic lesions. The scores for number of osteolytic lesions in each region were coded as: no lesions = 0, one lesion = 1, two lesions = 2, three to five lesions = 3, five to ten lesions = 4, and more than ten lesions = 5. Similarly, the scores for size of lesions were coded as: no lesions = 0, <1 cm = 1, 1-2 cm = 2, 2-4 cm = 3 and >4 cm = 4. The two scores summed up to an osteolytic score for each region and was subtracted by 1 in order to be continuous (value 0 to 8). The scores of all ten regions summed up to a total osteolysis score. The presence of radiological assessed osteoporosis was assigned score 1. Finally, each vertebral or non-vertebral fracture was assigned score 1 and summed up to a vertebral and a non-vertebral fracture score, respectively.

. Additional bone radiographs were taken as indicated by symptoms.

Before unblinding the trial, questionnaires on BON were completed by the individual principal investigator in each center, and the date of any BON diagnosis was registered.

The analysis of data was performed after the last included patient had been followed for at least 12 months. Overall survival (OS) data were updated in February and March 2009 by consulting the National Population Registries of the three participating Nordic countries.

Outcome measures and calculation of study sample size

The primary outcome measure was physical function estimated by EORTC QLQ-C30 questionnaire at 12 months after starting pamidronate treatment. In a previous study(20) 17% of patients responding to antimyeloma treatment and 26% of non-responders scored below 40 on the 0 – 100 physical functioning scale at 12 months. The sample size was estimated to detect a difference of comparable magnitude. Thus

an odds ratio of 1.76 for categorical data analysis formed the basis for estimating the necessary number of randomized patients, giving 250 in each group (90% power, α=0.05)(21).

Secondary outcome measures were skeletal related events (SRE) (time-to-first SRE, and number and type of event), skeletal event free survival(22)(survival without skeletal events), progression-free survival (PFS), OS, and quality of life outcomes (in particular, fatigue and pain). In the event of documented differences with respect to the primary end-point or skeletal events, a cost-utility analysis was planned.

Role of the funding source. The funding sponsors had no role in any part of the study and had no access to data or report writing.

Statistical analysis

Cross-sectional analyses of patient-reported outcomes at 12 months, as specified in the trial protocol, were made using t-tests. Also in accordance with the pre-specified protocol analyses, generalized estimating equations (GEE) were used: these make full use of the repeated three-monthly measures, and allow for the within-patient correlations over successive time points. Analyses were carried out using the observed values of the QLQ-C30 scores with baseline (pre-randomization) scores as covariates, which is equivalent to examining 'change from baseline' for each patient. The randomization stratification factors (planned treatment, WHO PS, beta-2 microglobulin) and baseline characteristics (age, gender and international staging system (ISS)) were evaluated for prognostic significance for each outcome, and where significant they were explored as covariates. Since the results were in all cases closely similar, only the baseline-adjusted analyses are presented. In order to investigate the impact of potential bias from missing data, multiple imputation with four repeats was explored using the ICE and MIM programs and predictive factors as above(23;24). This assumes that data are either missing at random (MAR) or

missing completely at random (MCAR), and uses an iterative multivariable switching regression to impute an estimated "best guess" for the missing observations, based on the identified prognostic factors. The regression model for QLQ-C30 items and scales was ordered logistic, and imputations were terminated at date of death, on grounds that quality of life after death is a meaningless concept, and that we are only interested in the QLQ scores in the living. The augmented dataset was analysed using GEE, however, which in effect assumes MCAR after death.

Survival curves were consistent with proportional hazards, and so Cox-models were used on an intention-to-treat basis. Log-rank tests were also used to confirm the overall significance tests. Ninety-five % confidence intervals (CIs) were calculated. In the survival analysis of SRE patients with no reported SRE were treated as censored at the date of last contact or , in the case of deaths, at date of death. All analyses were carried out using STATA version 10(25).

Results

Five hundred and four patients were included and randomized in the trial (252 patients in each group)(Figure 1). Two hundred and thirteen patients received MP- or MP-like treatment with or without addition of thalidomide and 289 patients induction therapy with VAD or Cyclophosphamide-Dexametasone to be followed by high-dose Melphalan and ASCT. The median follow up time from randomization was 3.4 years (range: 1.1 to 5.7). Baseline characteristics of the two treatment groups are summarized in Table 1 for the 502 patients where data was received, and show similar distribution of age, gender, planned treatment, WHO performance stage, Durie-Salmon staging, ISS, radiological bone disease, β-2-microglobulin, creatinine, and type of M protein.

	Pamidronate 90 mg Group P90 (N=250)	*Pamidronate 30 mg Group P30 (N=252)*
Age - median	62 years	63 years
< 60 years	97 (39%)	91 (36%)
60-69 years	81 (32%)	84 (33%)
70-79 years	57 (23%)	60 (24%)
80+ years	15 (6%)	17 (7%)
Gender		
Female	101 (40%)	97 (38%)
Male	149 (60%)	155 (62%)
Planned treatment		
MP-like	106 (42%)	107 (42%)
High-dose	144 (58%)	145 (58%)
WHO performance status		
0	38 (15%)	39 (15%)
1	58 (23%)	61 (24%)
2	62 (25%)	63 (25%)
3	57 (23%)	57 (23%)
4	17 (7%)	20 (8%)
unknown	18 (7%)	12 (5%)
Durie & Salmon staging		
I	46 (18%)	32 (13%)
II	68 (27%)	78 (31%)
III	126 (50%)	134 (53%)
Unknown	10 (4%)	8 (3%)
International Staging System		
1	56 (22%)	46 (18%)
2	99 (40%)	103 (41%)
3	62 (25%)	64 (26%)
Unknown	33 (12%)	39 (15%)
Skeletal morbidity(26)		
None	36 (14%)	27 (11%)
Limited	92 (37%)	106 (42%)
Osteoporosis	23 (9%)	19 (8%)
Extended	89 (36%)	88 (35%)
Unknown	10 (4%)	12 (4%)
β-2-microglobulin (mg/l)		
< 4	123 (49%)	106 (42%)
4-8	64 (26%)	79 (31%)
> 8	34 (14%)	33 (13%)
Unknown	29 (12%)	34 (14%)
S-creatinine (µmol/L)		
< 200	219 (88%)	226 (90%)
200+	31 (12%)	26 (10%)
M-protein		
IgA	53 (21%)	49 (19%)
IgD	0 (0%)	1 (0%)
IgE	1 (0%)	1 (0%)
IgG	143 (57%)	156 (62%)
Light-chain only	15 (6%)	16 (7%)
Unknown	38 (15%)	29 (12%)

Table 1. Baseline characteristics of newly diagnosed patients randomized to monthly infusions of pamidronate of 90 mg (P90) versus 30 mg (P30)

Quality of life

Ninety-five percent of the patients completed the first QLQ-C30 assessment. Of patients still alive at 12 months, 80.6 % (164/204) in group P90 and 84.2 % (171/203) in group P30 returned questionnaires. At 18 months more than 75 % of expected questionnaires were received. Five percent (22/487) of the patients had stopped their pamidronate treatment within the first 12 months (median 4.7 months). There was no significant difference in the primary outcome measure, physical function, neither at 12 months (mean: P90: 66, CI 62.9-70.0; P30: 68, CI 64.6-71.4, p=0.52) nor for the whole period (p=0.88). Physical function improved from the baseline value in both groups (Figure 2A). Other QLQ-C30 parameters showed a similar pattern (Figure 2B–D), with improvement of pain, fatigue and global health scores over time but with no significant difference between the two groups (at 12 months, pain score, p= 0.33; fatigue, p= 0.22; global health score, p=0.23; similar results when testing the whole period). These neutral results were confirmed when using imputation for missing observations.

Skeletal events

Time to first SRE. A total of 175 patients were reported to have at least one SRE (P90: 85, P30: 90). The first SREs in P90 and P30 respectively were: vertebral fractures (38, 40), surgically treated non-vertebral fractures (5, 5), irradiated osteolytic lesions (14, 12), new symptomatic osteolytic lesions (27, 28) and hypercalcemia (1, 5). The median time to first SRE was 9.0 months (0.95 CI: 8.3 -10.7) in those patients for whom an SRE was reported, with no statistical difference between the two groups (p= 0.63; hazard ratio 0.95, 95%CI 0.76–1.18) (Figure 3A). Figure 3B shows the time to first SRE stratified according to whether planned therapy was high-dose or MP-like (the median time to first SRE in those patients with reported SRE: P90: 9.0 months (CI: 7.3 -11.1) vs. P30: 10.0 months (CI: 8.2 - 10.7)). There was no overall significant difference between P90 and P30 (p=0.48), or any evidence that planned therapy affected the difference between P90 and P30 (interaction test, p=0.48).

Similarly, Figures 3C and 3D present the proportion of patients surviving without a skeletal event and show no significant difference (p=0.98; hazard ratio 1.0, 95%CI 0.81–1.23) between the two groups (median time P90: 21.4 months (CI: 15.8 – 28.9), P30: 22.1 months (CI: 19.3 – 28.0)).

Skeletal surveys at 9 and 24 months. Radiological findings at 9 months were reported from 116 out of 182 at risk in P90 and from 149 of 193 in P30. At 24 months there were radiological examinations in 71 of 113 in P90 and in 81 of 116 in P30. There was no significant difference between the two groups (Table 2). However, the number of x-rays reported (shown in Table 2) was significantly higher in the P30 group (P=0.005). Therefore the baseline characteristics has been explored using linear regression (for continuous outcomes) and logistic or ordered logistic regressions for categorical outcomes. Treatment and presence/absence of radiographs were modelled as main effects, and a treatment-by-radiograph interaction included. All characteristics of table 1 were explored, and in addition age, beta-2, serum creatinine, calcium, hb, and albumin were explored as continuous outcomes. Using a p-value of 0.05 for main effects and 0.01 for interactions, none of these factors were significantly related to presence/absence of radiographs. In terms of interaction effects, only beta-2 was significant with p=0.005, and this was only when treating beta-2 as a continuous variable. However, the results are not very striking. Further, given the multiplicity of testing (20 main effects for radiographs, and 20 interactions), at least one false positive is to be expected.

Radiographs were available for secondary centralized review by one radiologist from one third of the patients. Total osteolysis score was 11.0 in P90 and 10.0 in P30 at scheduled 9 months (p=1.00) and 12.0 in P90 and 13.0 in P30 at scheduled 24 months (p=0.69). The non-vertebral fracture score, vertebral fracture score and osteoporosis score did not show any difference between the two treatment groups.

	P90 (90 mg pamidronate) ***Number (percentage)***	***P30 (30 mg pamidronate)*** ***Number (percentage)***
9 months radiographs reported (reported/at risk)	116/182 (64%)	149/193 (77%)
Changes		
• progression	52 (44.8%)	50 (33.6%)
• regression	8 (6.9%)	13 (8.7%)
• unchanged	56 (48.3%)	86 (57.7%)
Number (average per patient)		
• vertebral fractures	43 (0.37)	35 (0.23)
• non-vertebral fractures	8 (0.07)	4 (0.02)
• new osteolytic lesion	43 (0.37)	31 (0.21)
24 months radiographs reported (reported/at risk)	71/113 (63%)	81/116 (70%)
Changes		
• progression	32 (45.1%)	40 (49.4%)
• regression	4 (5.6%)	2 (2.5%)
• unchanged	35 (49.3%)	39 (48.1%)
Number (average per patient)		
• vertebral fractures	37 (0.52)	45 (0.56)
• non-vertebral fractures	11 (0.15)	5 (0..06)
• new osteolytic lesion	38 (0.54)	40 (0.49)

Table 2. Reported findings from x-rays at 9 and 24 months.

Height decreases with time but there was no difference between the two groups (p>0.21).

Adverse events

Renal insufficiency. Fifteen patients from P90 and 7 patients from P30 were excluded due to increasing creatinine. This difference was not significant (p= 0.072). The time to more than 15 % increase in creatinine compared to baseline showed no significant difference between the two treatment groups (p= 0.48).

Osteonecrosis of the jaw. The BON questionnaires were returned for 76% (382/504) of the patients. Eight P90 patients developed BON 9 to 50 months after starting treatment compared to two P30 patients after 31 and 40 months. Kaplan Meier plots and analysis of the number of patients without BON showed no statistical differences though there appeared to be a trend toward increased risk in P90 (p=0.087). The cumulative doses of pamidronate in the patients with BON were 480 to 5220 mg (median: 2790 mg).

Myeloma disease

During the study period there were 201 deaths. One hundred and twenty-one were due to progressive disease, 8 from end-stage uremia without disease progression, 40 from infections and 32 for various reasons (myocardial infection, hemorrhage, other malignancy, unknown reasons). At the updated survival analysis 317 patients had died.

Response There were no significant differences in response to initial treatment between the groups (p=0.85). The response rates in P90 were: CR 0.19 (48/252) , PR 0.51 (128/252), MR 0.10 (25/252), NR 0.04 (10/252) and non-evaluable 0.16 (41/252), while in P30: CR 0.19 (49/252), PR 0.47 (118/252), MR 0.10 (24/252), NR 0.06 (14/252), and non-evaluable 0.18 (47/252))

Overall survival (Fig 4A). There was no significant difference in OS between the two groups (P=0.63). The median OS for patients planned for MP-like treatment or high-dose therapy was 28 months (CI: 22.9 - 34.1) and 68 months (CI: 53.1 - 78.9), respectively (p=0.001). There was no significant difference between P90 and P30 in these two groups of patients (p=0.54 by interaction test) (Median OS: P90 42 months (CI: 33.2 - 50.3), P30: 48 months (CI: 39.3 - 54.0).

Progression-free survival (Fig 4B). The median overall PFS was 22 months (CI: 19.5 - 26.3). There was no significant difference between the two groups (p=0.51), (P90: 21 months (CI: 15.8 - 28.9), P30: 22 months (CI: 19.3 - 28.0)). The median PFS for patients planned for MP-like treatment or high-dose therapy was 16 months (CI: 11.8 - 21.0) and 32 months (CI: 22.6 - 42.8), respectively (p=0.001).

Discussion

In this randomized double-blind multicentre phase 3 trial 90 mg of pamidronate was not significantly more effective than 30 mg in newly diagnosed myeloma patients, as assessed by patient-reported quality of life as well as by evaluation of skeletal events and height reduction. There was a non-significant tendency to fewer cases of BON and patients stopping pamidronate treatment due to nephrotoxicity among patients treated with 30 mg pamidronate. The dose given to individual patients was unknown to both investigators and patients until the analyses were completed. Although the use of other medications e.g. opioids, was not reported the blinded randomized design makes it unlikely that there are systematic differences between the groups..

To our knowledge, this is the first randomized blinded head-to-head trial comparing two doses of pamidronate for bone disease prophylaxis in newly diagnosed myeloma patients, and the first trial to use quality of life assessment as basis for evaluation of efficacy. The primary outcome was physical function estimated by the EORTC QLQ-C30 questionnaire, and showed no significant difference between 30 and 90 mg pamidronate given intravenously every 4 weeks. Other QLQ-C30 outcomes were also similar in the two treatment groups, although there was a general improvement of all outcomes over time compared to baseline indicating the expected effect of anti-myeloma treatment in newly diagnosed patients. We have previously shown that the EORTC QLQ-C30 is an important and reliable tool to evaluate the changes in quality of life with response to treatment and disease progression(27;28). The

present trial was designed to document any clinical relevant difference, but there was not even a suggestion of a difference in the quality of life whether treating with 30 mg or 90 mg pamidronate. Berenson et al.(4) have previously reported improved quality of life using pain score and a quality of life index (Spitzer index), systematically calculated based on an estimation by the physician (29). In contrast, the EORTC questionnaire is completed independently by the patients themselves. In the first clodronate trial (Finnish Leukaemia Group) no significant difference was found with respect to pain score although there was a suggestion that fewer patients in the placebo group had no pain after the two-year treatment period(2). In the second clodronate trial (MRC) pain score and performance status were evaluated by the physician, but a quality of life assessment was not performed(3;30). Thus two placebo controlled trials showed improvement of pain score, performance status and in the pamidronate trial (Myeloma Aredia Study Group) also quality of life in the bisphosphonate treated patients. In the present trial neither pain nor quality of life assessed by the patients showed any difference between 30 mg or 90 mg pamidronate indicating that the maximal effect of bisphosphonates is obtained by doses that might even be lower than 30 mg intravenous pamidronate every month.

The present trial population included almost 60% planned to receive high-dose chemotherapy compared to 3% in the MRC trial(3)In the Berenson pamidronate trial it was not indicated whether patients had received high-dose therapy(4). High-dose chemotherapy prolongs the disease control significantly(31-33) and therefore the present population differs from the trial populations in the previous published placebo-controlled trials, which is the most likely explanation of the relatively low number of vertebral fractures reported... This effect could overshadow a minor effect of the pamidronate dose, but we did not see even a suggestion of a better effect of the 90 mg pamidronate compared with 30 mg on the quality of life. On the other hand the MRC IX trial also included patients treated with high-dose chemotherapy (7).

Both daily oral clodronate and monthly intravenous pamidronate have proved significantly better than placebo in preventing skeletal events in randomized clinical trials(2-5). The development of more potent bisphosphonates was expected to improve the prophylactic effect on the skeletal disease in multiple myeloma. Zoledronic acid now seems more effective than clodronate in multiple myeloma (7). Zoledronic acid 4 mg was also more effective than pamidronate 90 mg as monthly infusions in patients with breast cancer but not in myeloma patients(6). The reason for different effects in these two patient groups is unknown, but it may be a result of differences in their skeletal disease. The significance of the osteoblast inhibition may dominate in multiple myeloma(1;34), leading only to osteolytic lesions, while the mixed picture of osteosclerotic and osteolytic bone metastases in breast cancer indicates a different mechanism of their bone disease(35;36). Our results show no significant difference in the time to first skeletal event and the curves were superimposed both for patients planned to receive high-dose melphalan with stem cell support and for patients receiving MP-like regimens; therefore disease control can hardly play a major role in the effect of bisphosphonates. The local centralized evaluation of 9 and 24 months x-rays were unfortunately incomplete and therefore less valid than time to first skeletal event, however, it was not inconsistent with the conclusion.

In vitro results indicated an anti-myeloma effect of bisphosphonates by inducing apoptosis in a dose-dependent manner. The effect was more prominent with the most potent nitrogen-containing bisphosphonates(11). We found no dose depending effect of pamidronate on the survival in the present trial neither for the whole trial population nor for subgroups of patients planned to receive high-dose therapy or not. The improved survival in newly diagnosed myeloma patients by zoledronic acid compared with clodronate reported recently (7) does not exclude a similar effect by pamidronate as indicated by the in vitro studies (11). Future studies comparing different doses of pamidronate as well as zoledronic acid are needed to find the optimal bisphosphonate dose for both preventing bone disease and improving overall survival in multiple myeloma.

The association between BON and bisphosphonate therapy was recognized in about 2003. The present trial was planned at an earlier time and therefore no attempts had been made to prevent BON. Though our analysis was retrospective, with the risk of underestimating the number of BON, we found a cumulative risk of about 14% for those patients who continued monthly pamidronate. Two cases were reported from P30 mg and 8 from P90 mg group. In the recent MRC IX trial BON was reported in 3.5% of patients treated with zoledronic acid compared with 0.5% in the clodronate arm, but time to BON was not reported(7). In addition the present study registered more patients who discontinued the pamidronate treatment in the P90 group due to nephrotoxicity. Although these differences were not statistically significant, they suggest that the lowest efficient dose of bisphosphonate should be used.

Also our observations on nephrotoxicity favor the sought-for lower effective bisphosphonate doses. Although not statistically significant, the higher number of P90 patients removed from the trial because of increasing creatinine levels suggests a higher nephrotoxicity of 90 compared with 30 mg pamidronate.

Changing from 90 mg pamidronate or 4 mg zoledronic acid to 30 mg pamidronate is likely to reduce the cost of medication. In addition there might be some reduction of the expenses to treatment of BON, though the guidelines to prevent BON have already reduced the risk.

Strength of our study is the double blind placebo controlled design, the large number of patients and the use of a validated instrument for evaluation of quality of life with a high response rate. Limitations include that planned radiographs were not available in a proportion of the patients and that the influence of other medications could not be analysed. Also analysis of BON was based on retrospective data.

The results of this trial indicates that pamidronate 90 mg given monthly is not superior to 30 mg in preventing skeletal events or improving quality of life in patients with newly diagnosed multiple myeloma, and thus no further inhibition of the osteoclast by bisphosphonates can be achieved. The results of the MRC IX trial seem to indicate that 4 mg zoledronic acid is superior to oral clodronate including an improvement of survival in myeloma patients. There are presently no data published comparing the efficacy of 30 mg pamidronate with 4 mg zoledronic acid or oral clodronate and therefore firm recommendations can still not be given about the optimal use of bisphosphonates in myeloma. However we conclude that monthly infusions of 30 mg pamidronate is not inferior to 90 mg pamidronate and could be recommended for prevention of skeletal disease in myeloma patients.

Whether other osteoclast inhibitors like RANKL-Ab(37) or RANK-Fc(38) can increase the effect further remains to be shown. However, it seems likely that a complete prevention of skeletal events in multiple myeloma demands an abolition of the osteoblast inhibition, e.g. by antibody inhibition of DKK1(39), but no clinical data on this approach have been published.

Research in context:

All phase 3 trials to date (4-6) used a dose of 90 mg pamidronate, that has been stated as the recommended dose in guidelines (16). The present study shows in the first comparison of two dosis that the 90 mg pamidronte is not significantly more effective than 30 mg. Therefore we suggest that monthly 30 mg can be the recommended pamidronate dose for preventing multiple myeloma bone disease to reduce cost and toxicity.

The study was registered in ClinicalTrials.gov (Identifier: NCT00376883).

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Contributors:

PG, KC, IT, FW, PF, CG, JW, and JLN were involved in the conception and design of the study. PG, IT, FW, and PF were involved in the provision of study material or patients or data acquisition. PG, IT, KC, FW, JW, JLN, and PF were involved in data analysis and interpretation. PF was responsible for the statistical analysis. PG, KC, IT, FW, and PF were involved in drafting the article. AM, and NA were involved inthe scoring of revised x-rays. All authors were involved in writing or critical review of the draft report and all approved the final version. A full list of study investigators can be found in the webappendix.

Conflicts of interest:

PG received grant support from Janssen-Cilag, a speaker's bureau from Celgene, and fee as chairman of Data Monitoring Comitte of Bionvent. AW grant support from Janssen-Cilag, fees for consultancy from Janssen-Cilag and Pharmion, and fee for manuscript to Novartis. HHH has received fees for speaker's and travel expenses to ASH and EHA from Bristol Myers Squibb and Norvartis. Nordic Myeloma Study Group has received grant support from Janssen-Cilag, Celgene, Amgen, and Nordpharma. All other authors declared no conflicts of interest.. The corresponding author had full access to all of the data and the final responsibility to submit for publication. None of the funding source (NCU and J_C) had access to the raw data, or any role of data analysis and interpretation or preparation of the manuscript and have not had access to any version of the manuscript.

Reference List

(1) Tian E, Zhan F, Walker R, et al. The role of the Wnt-signalling antagonist DKK1 in the development of osteolytic bone lesions in multiple myeloma. N Engl J Med 2003;349:2483-94.

(2) Lahtinen R, Laakso M, Palva I, Virkkunen P, Elomaa I. Randomised, placebo-controlled multicentre trial of clodronate in multiple myeloma. Finnish Leukaemia Group. Lancet 1992 Oct 31;340(8827):1049-52.

(3) McCloskey EV, MacLennan IC, Drayson MT, Chapman C, Dunn J, Kanis JA. A randomized trial of the effect of clodronate on skeletal morbidity in multiple myeloma. MRC Working Party on Leukaemia in Adults. Br J Haematol 1998 Feb;100(2):317-25.

(4) Berenson JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. N Engl J Med 1996 Feb 22;334(8):488-93.

(5) Berenson JR, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. J Clin Oncol 1998 Feb;16(2):593-602.

(6) Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer 2003 Oct 15;98(8):1735-44.

(7) Morgan G, Davies F, Gregory W, et al. Evaluating the effects of zoledronic acid (ZOL) on overall survival (OS) in patients (Pts) with multiple myeloma (MM): Results of the Medical Research Council (MRC) Myeloma IX study. J.Clin.Oncol. 28[15 May 20 Supplement]. 2010. Ref Type: Abstract

(8) Abildgaard N, Brixen K, Eriksen EF, Kristensen JE, Nielsen JL, Heickendorff L. Sequential analysis of biochemical markers of bone resorption and bone densitometry in multiple myeloma. Haematologica 2004 May;89(5):567-77.

(9) Terpos E, Politou M, Szydlo R, et al. Autologous stem cell transplantation normalizes abnormal bone remodeling and sRANKL/osteoprotegerin ratio in patients with multiple myeloma. Leukemia 2004 Aug;18(8):1420-6.

(10) Politou MC, Heath DJ, Rahemtulla A, et al. Serum concentrations of Dickkopf-1 protein are increased in patients with multiple myeloma and reduced after autologous stem cell transplantation. Int J Cancer 2006 Oct 1;119(7):1728-31.

(11) Shipman CM, Rogers MJ, Apperley JF, Russell RG, Croucher PI. Bisphosphonates induce apoptosis in human myeloma cell lines: a novel anti-tumour activity. Br J Haematol 1997 Sep;98(3):665-72.

(12) Aparicia A, Gardner A, Tu Y, Savage A, Berenson J, Lichetenstein A. *In vitro* cytoreductive effects on multiple myeloma cells induced by bisphosphonates. Leukemia 1998;12:220-9.

(13) Shipman CM, Vanderkerken K, Rogers MJ, et al. Short Report: The potent bisphosphonate ibandronate does not induce myeloma cell apoptosis in a murine model of established multiple myeloma. Br J Haematol 2000 Oct;111(1):283-6.

(14) Markowitz GS, Appel GB, et al. Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. J Am Soc Nephrol 2001 Jun;12(6):1164-72.

(15) Migliorati CA, Schubert MM, Peterson DE, Seneda LM. Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: an emerging oral complication of supportive cancer therapy. Cancer 2005 Jul 1;104(1):83-93.

(16) Terpos E, Sezer O, Croucher PI, et al. The use of bisphosphonates in multiple myeloma: recommendations of an expert panel on behalf of the European Myeloma Network. Ann Oncol 2009 May 22, 20(8): 1303-17..

(17) Mellqvist UH, Lenhoff S, Johnsen HE, et al. Cyclophosphamide plus dexamethasone is an efficient initial treatment before high-dose melphalan and autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of a randomized comparison with vincristine, doxorubicin, and dexamethasone. Cancer 2008 Jan 1;112(1):129-35.

(18) Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology
23. J Natl Cancer Inst 1993 Mar 3;85(5):365-76.

(19) Clemons M, Dranitsaris G, Cole D, Gainford MC. Too much, too little, too late to start again? Assessing the efficacy of bisphosphonates in patients with bone metastases from breast cancer. Oncologist 2006 Mar;11(3):227-33.

(20) Wisloff F, Gulbrandsen N. Health-related quality of life and patients' perceptions in interferon-treated multiple myeloma patients. Nordic Myeloma Study Group. Acta Oncol 2000;39(7):809-13.

(21) Campbell MJ, Julious SA, Altman DG. Estimating sample sizes for binary, ordered categorical, and continuous outcomes in two group comparisons. BMJ 1995 Oct 28;311(7013):1145-8.

(22) Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood 2006 Nov 15;108(10):3289-94.

(23) Royston P. Multiple imputation of missing values. Stata Journal 2004 Mar 15;4:227-41.

(24) Carlin JB, Li N, Greenwood P, Coffey C. Tools for analyzing multiple imputed datasets. Stata Journal 2003 May;3:226-44.

(25) Stata Statistical Software: Release 10, College Station [computer program]. StataCorp LP; 2007.

(26) Jacobson JL, Hussein MA, Barlogie B, Durie BG, Crowley JJ. A new staging system for multiple myeloma patients based on the Southwest Oncology Group (SWOG) experience 1. Br J Haematol 2003 Aug;122(3):441-50.

(27) Wisloff F, Hjorth M. Health-related quality of life assessed before and during chemotherapy predicts for survival in multiple myeloma. Nordic Myeloma Study Group. Br J Haematol 1997 Apr;97(1):29-37.

(28) Wisloff F, Eika S, Hippe E, et al. Measurement of health-related quality of life in multiple myeloma. Nordic Myeloma Study Group. Br J Haematol 1996 Mar;92(3):604-13.

(29) Spitzer WO, Dobson AJ, Hall J, et al. Measuring the quality of life of cancer patients: a concise QL-index for use by physicians. J Chronic Dis 1981;34(12):585-97.

(30) McCloskey EV, Dunn JA, Kanis JA, MacLennan IC, Drayson MT. Long-term follow-up of a prospective, double-blind, placebo-controlled randomized trial of clodronate in multiple myeloma. Br J Haematol 2001 Jun;113(4):1035-43.

(31) Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med 1996 Jul 11;335(2):91-7.

(32) Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003 May 8;348(19):1875-83.

(33) Lenhoff S, Hjorth M, Holmberg E, et al. Impact on survival of high-dose therapy with autologous stem cell support in patients younger than 60 years with newly diagnosed multiple myeloma: a population-based study. Nordic Myeloma Study Group. Blood 2000 Jan 1;95(1):7-11.

(34) Haaber J, Abildgaard N, Knudsen LM, et al. Myeloma cell expression of 10 candidate genes for osteolytic bone disease. Only overexpression of DKK1 correlates with clinical bone involvement at diagnosis. Br J Haematol 2008 Jan;140(1):25-35.

(35) Zheng Y, Zhou H, Fong-Yee C, Modzelewski JR, Seibel MJ, Dunstan CR. Bone resorption increases tumour growth in a mouse model of osteosclerotic breast cancer metastasis. Clin Exp Metastasis 2008;25(5):559-67.

(36) Mercer RR, Miyasaka C, Mastro AM. Metastatic breast cancer cells suppress osteoblast adhesion and differentiation. Clin Exp Metastasis 2004;21(5):427-35.

(37) Body JJ, Facon T, Coleman RE, et al. A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. Clin Cancer Res 2006 Feb 15;12(4):1221-8.

(38) Sordillo EM, Pearse RN. RANK-Fc: a therapeutic antagonist for RANK-L in myeloma. Cancer 2003 Feb 1;97(3 Suppl):802-12.

(39) Yaccoby S, Ling W, Zhan F, Walker R, Barlogie B, Shaughnessy JD, Jr. Antibody-based inhibition of DKK1 suppresses tumor-induced bone resorption and multiple myeloma growth in vivo. Blood 2007 Mar 1;109(5):2106-11.

Figure 1. Flowchart of the progress through the phases of the trial.

Figure 2. Quality of life (QoL) outcomes estimated by EORTC QLQ-C30 every third month after randomization to intravenous pamidronate 90 mg (P90) versus 30 mg (P30). 1A shows physical function, 1B fatigue, 1C global health QoL, and 1D pain. Group P90 black solid line and group P30 broken red line. The 95% confidence limits are indicated.

* The QLQ-C30 assesses QoL during the past week, and is scored from 0 to 100 where 100 represents the highest (best) possible physical function and health status/QoL or the highest (worst) possible levels of pain and fatigue, and 0 indicates the lowest possible scores

Figure 3. Skeletal disease after randomization to intravenous pamidronate 90 mg (P90) versus 30 mg (P30). 3A and 3B show Kaplan Meier plot of time to first skeletal event and 3C and 3D skeletal event free survival. Group P90 solid black line and group P30 broken red line (3A and 3C) and in 3B and 3D the results for patients planned for MP-like treatment or high-dose melphalan with stem cell support (HDM+ASCT) (Group P90: MP-like solid black line and HDM+ASCT broken red line, Group P30: MP-like broken brown line and HDM+ASCT broken and dotted red line).

Figure 4. Overall survival (4A) and progression-free survival (4B) after randomization to intravenous pamidronate 90 mg (P90) versus 30 mg (P30). Group P90 black solid line and group P30 broken red line.