Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial

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Summary

Background Compared with placebo, prophylactic treatment with bisphosphonates reduces risk of skeletal events in patients with multiple myeloma. However, because of toxicity associated with long-term bisphosphonate treatment, establishing the lowest effective dose is important. This study compared the effect of two doses of pamidronate on health-related quality of life and skeletal morbidity in patients with newly diagnosed multiple myeloma.

Methods This double-blind, randomised, phase 3 trial was undertaken at 37 clinics in Denmark, Norway, and Sweden. Patients with multiple myeloma who were starting antimyeloma treatment were randomly assigned in a 1:1 ratio to receive one of two doses of pamidronate (30 mg or 90 mg) given by intravenous infusion once a month for at least 3 years. Randomisation was done by use of a central, computerised minimisation system. Primary outcome was physical function after 12 months estimated by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire (scale 0–100). All patients who returned questionnaires at 12 months and were still on study treatment were included in the analysis of the primary endpoint. This study is registered with ClinicalTrials.gov, number NCT00376883.

Findings From January, 2001, until August, 2005, 504 patients were randomly assigned to pamidronate 30 mg or 90 mg (252 in each group). 157 patients in the 90 mg group and 156 in the 30 mg group were included in the primary analysis. Mean physical function at 12 months was 66 points (95% CI 62·9–70·0) in the 90 mg group and 68 points (64·6–71·4) in the 30 mg group (95% CI of difference –6·6 to 3·3; p=0·52). Median time to first skeletal-related event in patients who had such an event was 9·2 months (8·1–10·7) in the 90 mg group and 10·2 months (7·3–14·0) in the 30 mg group (p=0·63). In a retrospective analysis, eight patients in the pamidronate 90 mg group developed osteonecrosis of the jaw compared with two patients in the 30 mg group.

Interpretation Monthly infusion of pamidronate 30 mg should be the recommended dose for prevention of bone disease in patients with multiple myeloma.

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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 that involve receptor activator for nuclear factor κB (RANK) and RANK ligand (RANKL), and simultaneously inhibit osteoblasts.[1] The result is progressive osteolytic bone lesions with bone pain, pathological fractures, and hypercalcaemia, all of which have a major effect 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 other malignant diseases with bone metastases. Initial randomised placebo-controlled trials showed substantial effects of oral clodronate[2,3] and intravenous pamidronate[4,5] on bone disease. In subsequent trials, the more potent zoledronic acid showed similar effects to pamidronate in patients with multiple myeloma.[6] With regard to the antiresorptive effect, the bisphosphonate dose intensity increases substantially from clodronate to pamidronate to zoledronic acid. Recently, the Medical Research Council (MRC) Myeloma IX trial showed that compared with clodronate, zoledronic acid improved skeletal-related events and overall survival in patients with newly diagnosed multiple myeloma.[7] However, the dose providing maximum prophylactic effect is not known. Although most trials have focused on skeletal events, few data have been published on prospective evaluation of quality of life.

Myeloma treatment itself has an important effect on bone disease; it leads to an increase in bone density in patients responding to conventional chemotherapy.[8]

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Furthermore, the combination of high-dose melphalan with autologous stem-cell transplantation and bisphosphonate treatment has been shown to normalise the dysregulation of RANKL, RANK,[9] and Dickkopf-1 protein.[10]

Laboratory studies have shown a direct and dose-dependent antimyeloma effect of bisphosphonates in cell lines,[11] whereas the in-vivo effect is less well documented.[12,13] Attempts to use higher doses of pamidronate and zoledronic acid had to be stopped because of an increased risk of renal impairment (eg, development of glomerulosclerosis) after treatment with pamidronate.[14] Long-term treatment with pamidronate and zoledronic acid seems to increase the risk of developing osteonecrosis of the jaw.[15] Because of increased awareness of long-term toxicity of bisphosphonates, recent recommendations restrict the time on treatment to 2 years.[16] Furthermore, to avoid toxic effects, the lowest effective dose of bisphosphonates needs to be explored.

The objective of this trial was to compare the effect of two doses of intravenous pamidronate (30 mg *vs* 90 mg) in previously untreated patients with multiple myeloma. Since the ultimate aim of bisphosphonate therapy is to improve quality of life, patient-reported physical function as determined by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire was chosen as the primary outcome measure. Skeletal events were analysed as a secondary outcome measure, and although not pre-planned, the trial also allowed retrospective assessment of the occurrence of osteonecrosis of the jaw.

Methods

Patients

For the **full protocol for this trial** see http://www.nordic-myeloma.org

Patients of any age with untreated symptomatic multiple myeloma presenting at 37 clinics in Denmark, Norway, and Sweden from January, 2001, until August, 2005, were eligible for enrolment in this double-blind, randomised, phase 3 trial. Exclusion criteria were P-creatinine higher than 400 µmol/L, expected survival less than 3 months, and previous treatment with bisphosphonates for more than two of the previous 6 months. Study medication was initiated within the first month of antimyeloma therapy. Patients whose planned therapy was high-dose melphalan followed by autologous stem-cell transplantation received vincristine, doxorubicin, and dexamethasone or cyclophosphamide and dexamethasone[17] as induction therapy. Patients not eligible for high-dose therapy were given melphalan and prednisone with or without thalidomide.

The trial was done in accordance with the Declaration of Helsinki and approved by ethics committees and health authorities in Denmark, Norway, and Sweden. All participants provided written informed consent. The data were monitored by the regional coordinators of the Nordic Myeloma Study Group.

Randomisation and masking

Patients were randomly allocated in a 1:1 ratio to receive one of two doses of pamidronate (30 mg or 90 mg; Aredia, Novartis Pharmaceuticals, New Jersey, USA) given by intravenous infusion for 2·5 h once every month. Clinical investigators at each site called the Copenhagen Trial Unit with information about patient data and stratification variables. The Copenhagen Trial Unit then undertook the central randomisation and sent the information to the drug distributor, Amgros (Copenhagen, Denmark). The centralised randomisation used a computerised minimisation system developed according to Pocock.[18] When the groups were completely balanced with respect to the minimisation criteria, a computer-based 1:1 randomisation was used. We stratified participants according to country (Sweden *vs* not Sweden), planned therapy (high-dose melphalan followed by autologous stem-cell transplantation *vs* treatment based on melphalan and prednisone), β2-microglobulin concentration (<2·6 mg/L *vs* ≥2·6 mg/L), WHO performance status (≤2 *vs* >2), and whether or not the patient was included in another Nordic myelomatosis trial (melphalan and prednisone with or without thalidomide). The drug distributor sent 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. Patients, doctors, and study investigators were masked to group assignment. After final approval of the collected data, the statistician was informed of the allocation groups. After statistical analysis was done, the Copenhagen Trial Unit unblinded the actual dose of the two groups.

Procedures

The treatment with pamidronate was continued for at least 3 years, with patients given the option to continue treatment thereafter. Quality of life was assessed by the EORTC QLQ-C30.[19] Questionnaires were given to patients at enrolment and subsequently sent directly to the patient every 3 months by post.

Patients were followed up every 3 months for assessment of disease status, skeletal events, height, and toxicity (including concentrations of creatinine and calcium). Skeletal events were defined as spontaneous fracture, new vertebral compression, new osteolytic lesions needing irradiation therapy or surgery,[4] symptomatic progression of known osteolytic lesions, or hypercalcaemia.[20] Skeletal survey was to be undertaken at baseline and after 9 months and 24 months. The local radiological departments reported their assessments: progression was defined as a 25% progression of existing osteolytic lesions or vertebral fractures, or development of new osteolytic lesions or fractures. Regression was defined as a more than 25% reduction in size of lesions or healing. All obtainable radiographs were collected,

and centrally reviewed by an experienced radiologist (who was masked to treatment assignment) to calculate arbitrary radiograph 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; less than 1 cm, 1; 1–2 cm, 2; 2–4 cm, 3; and more than 4 cm, 4. The sum of the two scores provided an osteolytic score for each region and was subtracted by 1 to be continuous (value 0 to 8). The sum of the scores from all ten regions provided a total osteolysis score. The presence of radiologically assessed osteoporosis was assigned a score of 1. Finally, each vertebral or non-vertebral fracture was assigned a score of 1 and added 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 about osteonecrosis of the jaw were completed by the individual principal investigator in each centre, and the date of any diagnosis of this disorder was registered.

Data analysis was done after the last included patient had been followed up for at least 12 months. Data for overall survival were updated in February and March, 2009, by consulting the national population registries of the three participating Nordic countries. When 200 patients had been followed up for 6 months, the independent monitoring and safety committee undertook an interim analysis for toxicity and concluded that the trial could continue.

The primary outcome measure was physical function estimated by the EORTC QLQ-C30 questionnaire at 12 months after the start of treatment. Secondary outcome measures were skeletal-related events (time-to-first skeletal-related event, and number and type of event), skeletal-event-free survival[21] (survival without skeletal events), progression-free survival, overall survival, and quality of life outcomes (in particular, fatigue and pain). In the event of documented differences with respect to the primary endpoint or skeletal events, a cost-utility analysis was planned.

Statistical analysis

In a previous study,[22] 17% of patients who responded to antimyeloma treatment and 26% of patients who did not respond scored below 40 on the 0–100 physical functioning scale of the EORTC QLQ-C30 questionnaire at 12 months. The sample size for this trial was estimated to detect a difference of similar magnitude. Thus, with an odds ratio of 1·76 for categorical data analysis, 250 patients in each group were needed to provide 90% power and an α level of 0·05.[23]

All patients who returned questionnaires at 12 months and were still on study treatment were included in the analysis of the primary endpoint. Cross-sectional analyses of patient-reported outcomes at 12 months, as specified in the trial protocol, were done by use of *t* tests. In accordance with the prespecified protocol analyses, generalised estimating equations were used: these equations make full use of the repeated 3-monthly measures, and allow for within-patient correlation over successive timepoints. Analyses were done with the observed values of the QLQ-C30 scores with baseline (pre-randomisation) scores as covariates, which is equivalent to examination of "change from baseline" for each patient. The randomisation stratification factors (planned treatment, WHO performance status, β2 microglobulin, and participation in another myelomatosis trial) and baseline characteristics (age, sex, and international staging system) were assessed for prognostic significance for each outcome; if significant, they were explored as covariates. Since the results were closely similar in all cases, only the baseline-adjusted analyses are presented. To investigate the effect of potential bias from missing data, multiple imputation with four repeats was done with ICE and MIM programs and the previously mentioned prognostic factors.[24,25] This approach assumes that data are either missing at random or missing completely at random, and uses an iterative multivariable switching regression to impute an

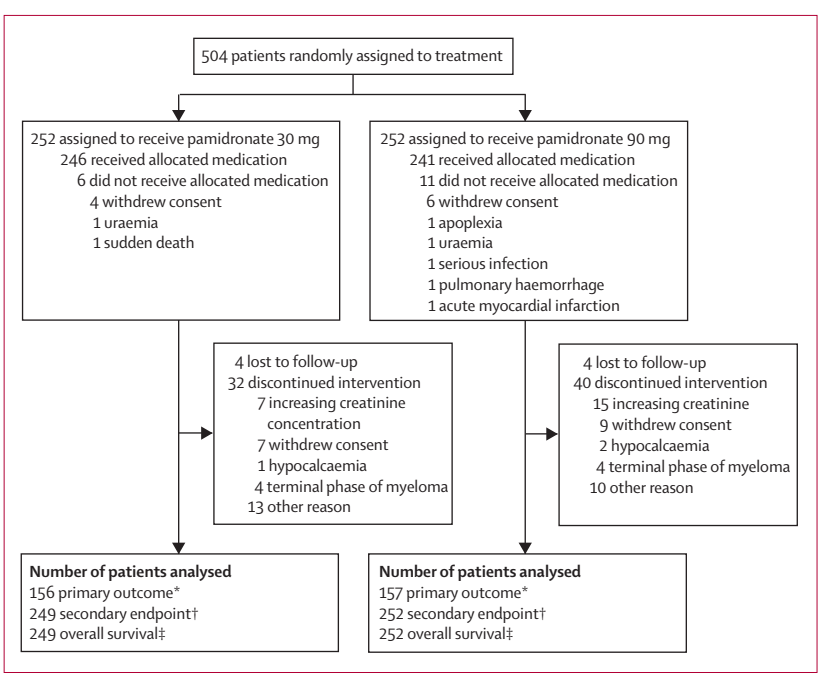

***Figure 1*: Trial profile**

Data for number of patients screened for eligibility were not gathered. *All patients who returned questionnaires at 12 months and were still on study treatment were included in the analysis of the primary endpoint. †All patients were included in the analysis of the secondary endpoint but were censored at the time of last report. Three patients from the pamidronate 30 mg group were missing all data and could not be retrieved in the national registries. ‡All patients were included in the analysis of overall survival, apart from the three patients who were missing all data.

	Pamidronate 90 mg (n=250)	Pamidronate 30 mg (n=252)
Age (years)	62 (35–87)	63 (37–92)
<60	97 (39%)	91 (36%)
60–69	81 (32%)	84 (33%)
70–79	57 (23%)	60 (24%)
≥80	15 (6%)	17 (7%)
Sex (male)	149 (60%)	155 (62%)
Planned treatment		
Based on melphalan and prednisone	106 (42%)	107 (42%)
High-dose melphalan followed by autologous stem-cell transplantation	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 (25%)
Unknown	33 (13%)	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 (5%)
β2 microglobulin (mg/L)		
<4	123 (49%)	106 (42%)
4–8	64 (26%)	79 (31%)
>8	34 (14%)	33 (13%)
Unknown	29 (12%)	34 (13%)
S-creatinine (μmol/L)		
<200	219 (88%)	226 (90%)
≥200	31 (12%)	26 (10%)
M protein		
IgA	53 (21%)	49 (19%)
IgD	0	1 (<1%)
IgE	1 (<1%)	1 (<1%)
IgG	143 (57%)	156 (62%)
Light-chain only	15 (6%)	16 (6%)
Unknown	38 (15%)	29 (12%)

Data are median (range) or number (%). Data were not available for two patients in the 90 mg group.

Table 1: **Baseline characteristics of study participants**

estimated "best guess" for the missing observations, on the basis of the identified prognostic factors. The regression model for QLQ-C30 items and scales was ordered logistically and imputations were terminated at date of death, since quality of life after death is a meaningless notion. The augmented dataset was analysed by use of generalised estimating equations; this approach assumes that data are missing completely at random after death.

Survival curves were consistent with proportional hazards; therefore, Cox models were used on an intention-to-treat basis. Log-rank tests were also used to confirm the overall significance tests. 95% CIs were calculated. In the survival analysis of skeletal-related events, patients with no reported events were treated as censored at the date of last contact or, in the case of deaths, at date of death. All analyses were done with STATA version 10.

All patients were included in the analysis of the secondary endpoint but were censored at the time of last report. All patients were included in the analysis of overall survival.

This study is registered with ClinicalTrials.gov, number NCT00376883.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 504 patients were enrolled and randomly assigned to receive pamidronate 90 mg or 30 mg (252 in each group). Table 1 shows baseline characteristics for the 502 randomised patients for whom data were available. Planned treatment was based on melphalan and prednisone with or without addition of thalidomide in 213 patients. 289 patients received induction therapy with vincristine, doxorubicin, and dexamethasone or cyclophosphamide and dexamethasone, followed by high-dose melphalan and autologous stem-cell transplantation. Median follow-up time was 3·4 years (range 1·1–5·7) from randomisation.

477 (95%) patients completed the first QLQ-C30 assessment. 164 (80%) of 204 patients still alive at 12 months returned questionnaires in the pamidronate 90 mg group compared with 171 (84%) of 203 in the 30 mg group. At 18 months, more than 75% of expected questionnaires had been received. 22 (5%) of 487 patients discontinued pamidronate treatment within the first 12 months (90 mg, seven patients; 30 mg, 15 patients); median time until discontinuation was 4·7 months (range 0·1–11·3).

The primary outcome measure, physical function, did not differ between groups either at 12 months (mean scores: 90 mg, 66 points, 95% CI 62·9–70·0; 30 mg,

68 points, 64·6–71·4; 95% CI of difference –6·6 to 3·3, p=0·52) or for the whole period (p=0·88). Physical function improved from the baseline value in both groups (figure 2). Other QLQ-C30 measures showed a similar pattern (figure 2), with improvement of pain, fatigue, and global health scores over time, but with no significant difference between groups (difference between groups at 12 months, pain score, p=0·33; fatigue, p=0·22; global health score, p=0·23; similar results were obtained for the whole study period). Similar findings were seen when imputation for missing observations was used in the analysis.

175 patients had at least one skeletal-related event (90 mg, n=85 *vs* 30 mg, n=90). First skeletal-related events were vertebral fractures (n=38 *vs* n=40), surgically treated non-vertebral fractures (five patients in each group), irradiated osteolytic lesions (n=14 *vs* n=12), new symptomatic osteolytic lesions (n=27 *vs* n=28), and hypercalcaemia (one patient *vs* five patients). Median time to first skeletal-related event was 9·0 months (95% CI 8·3–10·7) in patients for whom a skeletal-related event was reported, with no statistical difference between groups (90 mg, 9·2 months, 8·1–10·7; 30 mg, 10·2 months, 7·3–14·0; p=0·63; hazard ratio [HR] 0·95, 95% CI 0·76–1·18; figure 3A). Figure 3B shows the time to first skeletal-related event stratified according to whether planned therapy was high-dose melphalan followed by autologous stem-cell transplantation or based on melphalan and prednisone (median time to first skeletal-related event in those patients with a reported event: 90 mg, 9·0 months, 95% CI 7·3–11·1; 30 mg, 10·0 months, 8·2–10·7). There was no overall significant difference between groups (p=0·32), nor any evidence that planned therapy affected the difference between groups (interaction test, p=0·48).

The proportion of patients surviving without a skeletal event did not differ between groups (p=0·98; HR 1·0, 95% CI 0·81–1·23; median time: 90 mg, 21·4 months, 95% CI 15·8–28·9; 30 mg, 22·1 months, 19·3–28·0).

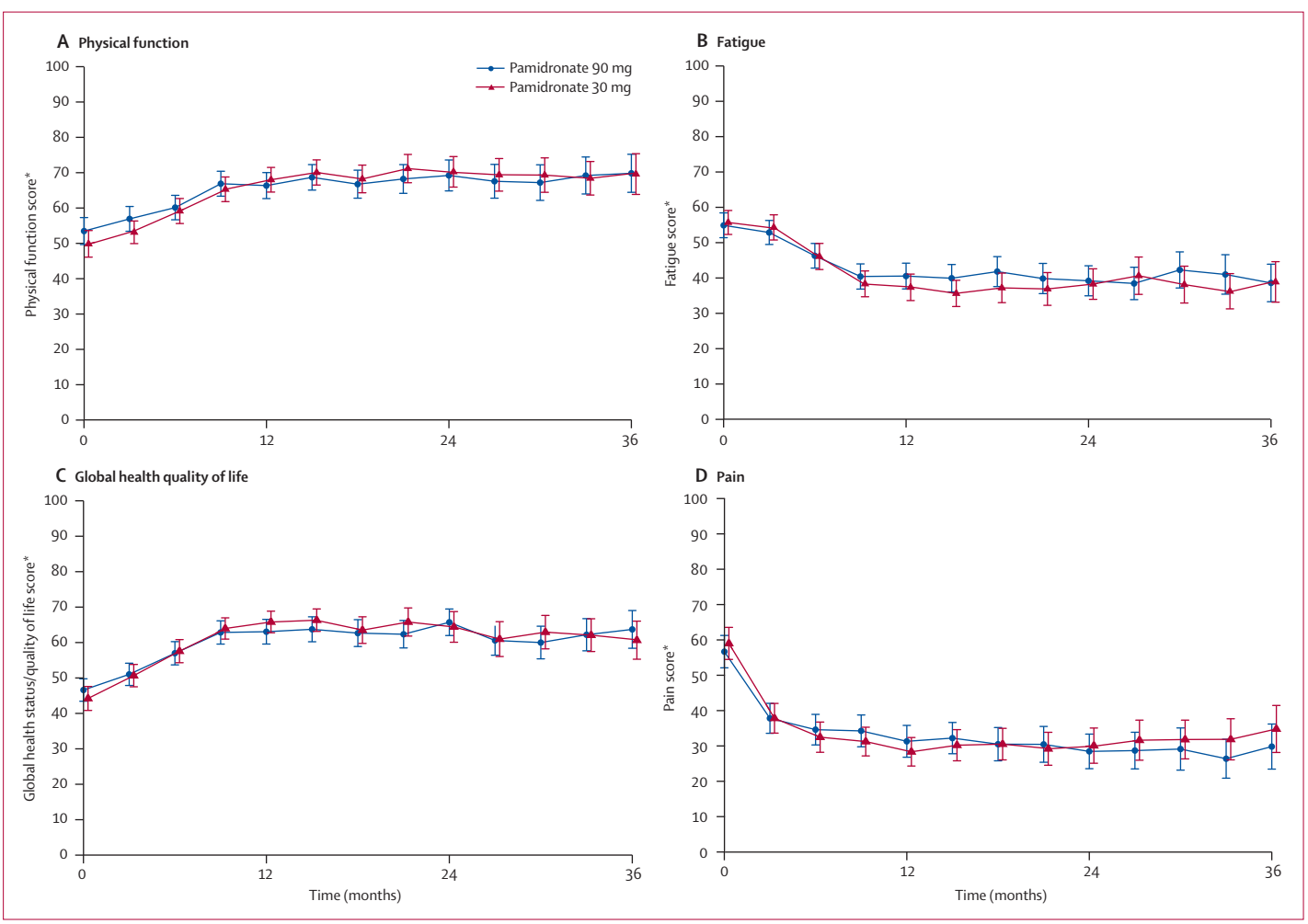

Figure 2: **Quality of life outcomes**
Outcomes were estimated by the European Organisation for Research and Treatment of Cancer QLQ-C30 every 3 months after randomisation. Error bars represent 95% CIs. *The QLQ-C30 assesses quality of life during the previous week, and is scored from 0 to 100, where 100 represents the highest (best) possible physical function and health status/quality of life or the highest (worst) possible levels of pain and fatigue, and 0 indicates the lowest possible scores.

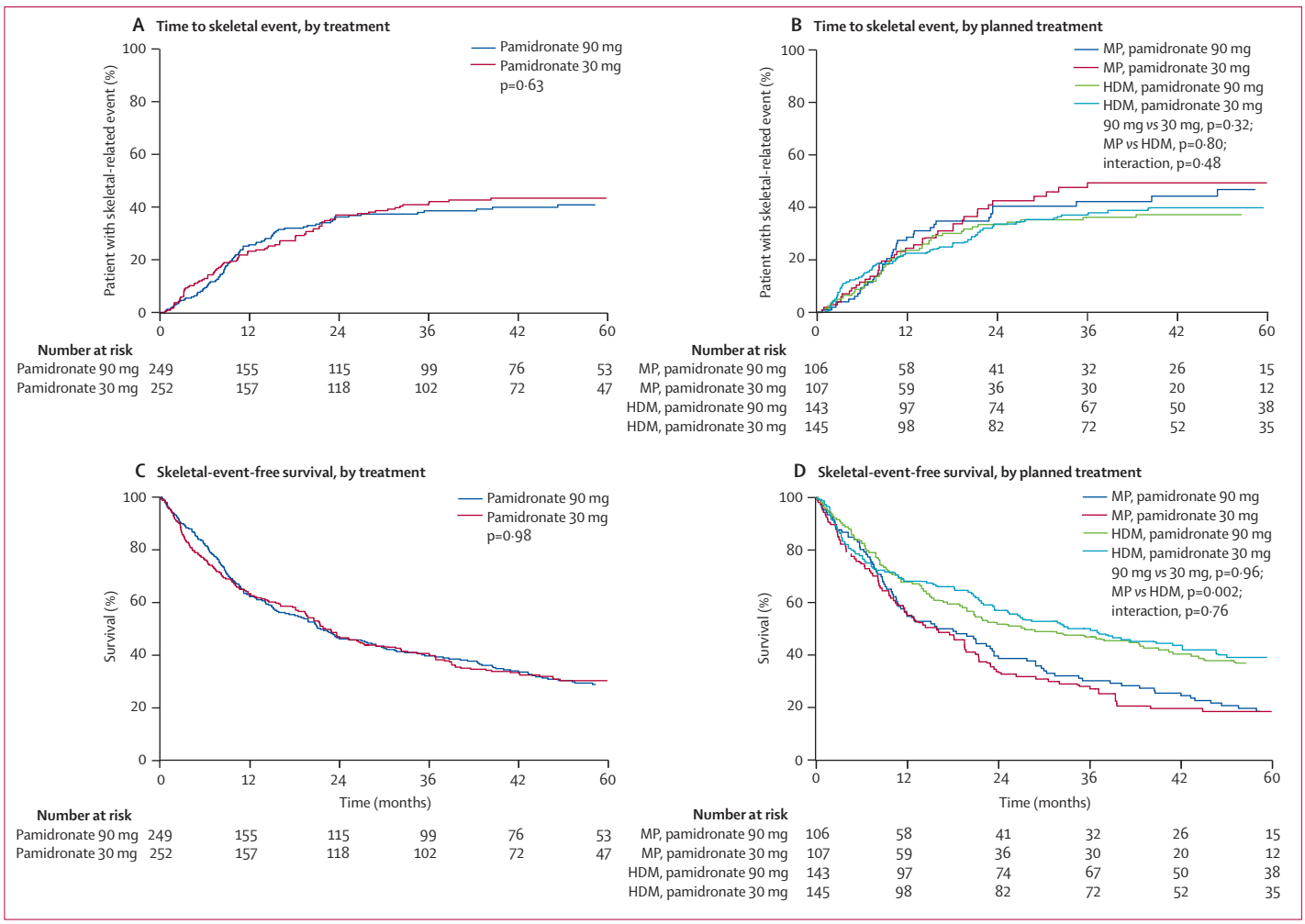

Figure 3: **Skeletal disease**
(A) and (B) show Kaplan-Meier plots of time to first skeletal event. (C) and (D) show skeletal-event-free survival. In (B) and (D), results are shown by planned treatment (treatment based on melphalan and prednisone [MP] or high-dose melphalan followed by autologous stem-cell transplantation [HDM]).

Radiological findings did not differ between groups (table 2). However, the number of radiographs reported was significantly higher in patients assigned to pamidronate 30 mg than in those assigned to 90 mg (p=0·005 for comparison at 9 months; table 2). Therefore, baseline characteristics were explored by use of linear regression (for continuous outcomes) and logistic or ordered logistic regressions for categorical outcomes. Treatment and presence or absence of radiographs were modelled as main effects, and a treatment-by-radiograph interaction included. All characteristics shown in table 1 were explored; additionally, age, β2 microglobulin, serum creatinine, calcium, haemoglobin, and albumin were explored as continuous outcomes. With a p value of 0·05 for main effects and 0·01 for interactions, none of these factors were significantly related to presence or absence of radiographs. In terms of interaction effects, only β2 microglobulin was significant (p=0·005), and this result only occurred when β2 microglobulin was treated as a continuous variable. However, the results are not very striking. Furthermore, in view of the multiplicity of testing (20 main effects for radiographs, and 20 interactions), at least one false positive is to be expected.

Radiographs from 154 (31%) patients (90 mg, 72 patients; 30 mg, 82 patients) were available for secondary centralised review by one radiologist. Total osteolysis score was 11·0 in those assigned to pamidronate 90 mg and 10·0 in those assigned to pamidronate 30 mg at 9 months (p=1·00) and 12·0 and 13·0 at 24 months, respectively (p=0·69). Non-vertebral fracture score, vertebral fracture score, and osteoporosis score did not differ between groups (data not shown).

Height decreased with time but there was no difference between the two groups (data not shown; p>0·11 at all timepoints up to 4 years).

15 patients assigned to pamidronate 90 mg and seven patients assigned to pamidronate 30 mg were excluded because of an increase in creatinine concentration

	Pamidronate 90 mg	Pamidronate 30 mg
9 months		
Number at risk	182	193
Radiographs reported	116 (64%)	149 (77%)
Changes		
Progression	52 (44·8%)	50 (33·6%)
Regression	8 (6·9%)	13 (8·7%)
Unchanged	56 (48·3%)	86 (57·7%)
Number of events (median per patient)		
Vertebral fractures	43 (0·37)	35 (0·23)
Non-vertebral fractures	8 (0·07)	4 (0·02)
New osteolytic lesions	43 (0·37)	31 (0·21)
24 months		
Number at risk	113	116
Radiographs reported	71 (63%)	81 (70%)
Changes		
Progression	32 (45·1%)	40 (49·4%)
Regression	4 (5·6%)	2 (2·5%)
Unchanged	35 (49·3%)	39 (48·1%)
Number of events (median per patient)		
Vertebral fractures	37 (0·52)	45 (0·56)
Non-vertebral fractures	11 (0·15)	5 (0·06)
New osteolytic lesions	38 (0·54)	40 (0·49)

Data are number (%) unless otherwise indicated.

Table 2: **Reported findings from radiographs at 9 months and 24 months**

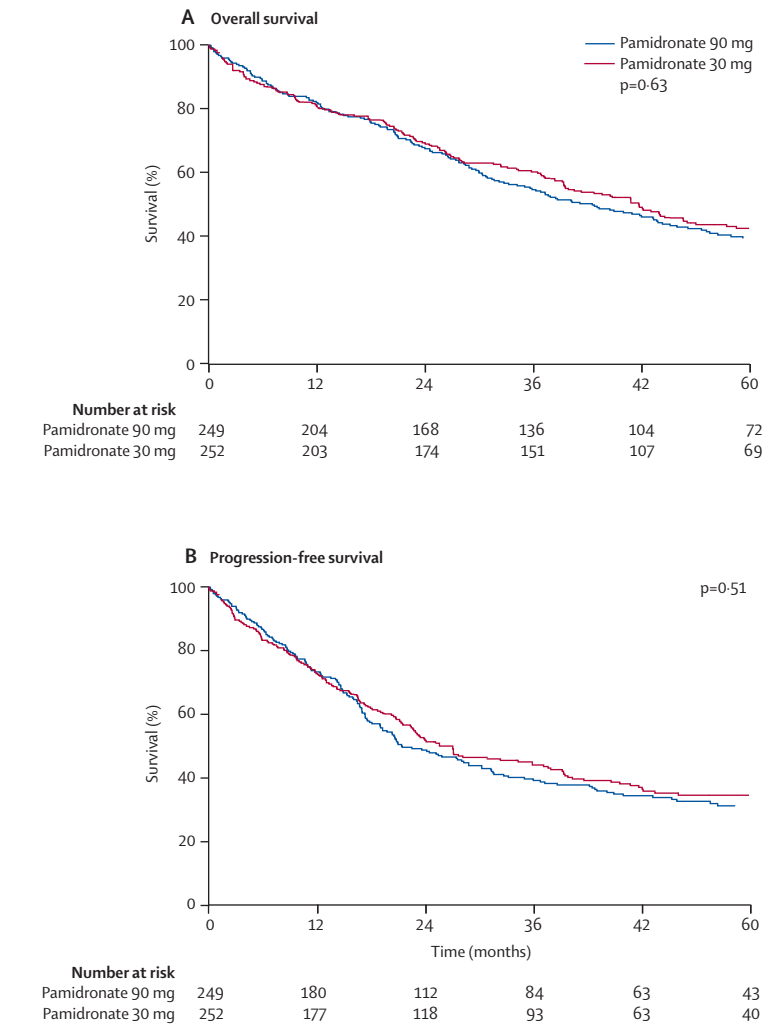

Figure 4: **Overall survival and progression-free survival**

(difference between groups p=0·072). Median time taken to reach a more than 15% increase in creatinine concentration compared with baseline did not differ between groups (90 mg, median 10·7 months, 95% CI 8·4–15·2; 30 mg, 14·8 months, 11·1–18·0; p=0·48).

Questionnaires about osteonecrosis of the jaw were returned from 382 (76%) of the 504 randomised patients. Eight patients in the 90 mg group developed osteonecrosis of the jaw up to 50 months after starting treatment compared with two patients in the 30 mg group who developed this disorder after 31 months and 40 months. Kaplan-Meier plots and analysis of the number of patients without osteonecrosis of the jaw showed no differences between groups, although there seemed to be a trend towards increased risk in patients assigned to pamidronate 90 mg (p=0·087). The cumulative dose of pamidronate in patients with osteonecrosis of the jaw was 480–5220 mg (median 2790 mg for all patients; 90 mg, 3780 mg; 30 mg, 765 mg).

During the study period there were 201 deaths. 121 deaths were caused by progressive disease, eight from end-stage uraemia without disease progression, 40 from infections, and 32 for other reasons (myocardial infection, haemorrhage, other malignancy, unknown reasons). At the updated survival analysis, 317 patients had died.

There were no significant differences in response to initial treatment between groups (p=0·85). The response rates in the 90 mg group were complete response 19% (48 of 252 patients), partial response 51% (128 patients), minor response 10% (25 patients), no response 4% (ten patients) and non-evaluable 16% (41 patients). In the 30 mg group, rates were complete response 19% (49 of 252 patients), partial response 47% (118 patients), minor response 10% (24 patients), no response 6% (14 patients), and non-evaluable 19% (47 patients).

Overall survival did not differ between treatment groups (p=0·63; figure 4). Median overall survival was 28 months (95% CI 22·9–34·1) in patients whose planned treatment was based on melphalan and prednisone and 68 months (53·1–78·9) in those whose planned treatment was high-dose melphalan followed by autologous stem-cell transplantation (p=0·001). There was no significant difference between assignment to pamidronate 90 mg and 30 mg in these two groups of patients (p=0·54 by interaction test; median overall survival: 90 mg, 42 months, 33·2–50·3; 30 mg, 48 months, 39·3–54·0).

Median overall progression-free survival was 22 months (95% CI 19·5–26·3); 21 months (15·8–28·9) in the 90 mg group compared with 22 months (19·3–28·0) in the 30 mg group (p=0·51; figure 4). Median progression-free survival was 16 months (11·8–21·0) in patients whose planned treatment was based on melphalan and prednisone and 32 months (22·6–42·8) in those whose planned treatment was high-dose melphalan followed by autologous stem-cell transplantation (p=0·001).

Discussion

In this double-blind, randomised, phase 3 trial, 90 mg pamidronate was not significantly more effective than 30 mg for improvement of quality of life in patients with newly diagnosed myeloma. Fewer patients in the 30 mg group developed osteonecrosis of the jaw or discontinued pamidronate because of nephrotoxicity than did patients in the 90 mg group. The dose given to individual patients was unknown to both investigators and patients until the analyses were completed. Although use of other medications (eg, opioids) was not reported, the double-blind, randomised study design makes systematic differences between the groups unlikely.

To our knowledge, this is the first randomised, blinded, head-to-head trial comparing two doses of pamidronate for prophylaxis of bone disease in patients with newly diagnosed myeloma (panel). It is also the first trial of pamidronate to use quality of life assessment as the basis for evaluation of efficacy. The primary outcome, physical function at 12 months, and other QLQ-C30 outcomes did not differ between groups. However, there was a general improvement of all outcomes over time compared with baseline, indicating the expected effect of antimyeloma treatment in newly diagnosed patients. We have previously shown that the EORTC QLQ-C30 questionnaire is an important and reliable method for assessment of changes in quality of life with response to treatment and disease progression.[27,28] Berenson and colleagues[4] previously reported improved quality of life in patients with newly diagnosed or second-line-treated multiple myeloma who were treated with pamidronate, as determined by pain scores and a quality of life index (Spitzer index), systematically calculated on the basis of an estimation by the physician.[29] By contrast, the EORTC questionnaire is completed independently by the patients. In the first trial of clodronate (Finnish Leukaemia Group),[2] pain score did not differ between intervention and placebo groups; however, there was a suggestion that fewer patients in the placebo group had no pain after the 2-year treatment period than did patients assigned to the intervention. In the second clodronate trial (MRC), pain score and performance status were assessed by the physician, but quality of life was not assessed.[3,30] In the pamidronate trial (Myeloma Aredia Study Group),[5] bisphosphonate improved quality of life compared with placebo. In our trial, neither pain nor quality of life as assessed by the patients showed any difference between the 90 mg and 30 mg pamidronate groups. This result suggests that bisphosphonates might be most effective when given at doses that are even lower than 30 mg per month.

60% of patients in this trial were planned to receive high-dose chemotherapy compared with 3% in the MRC trial.[3] The trial by Berenson and colleagues[4] did not report whether patients had received high-dose therapy. High-dose chemotherapy substantially extends disease control[31–33] and therefore the population of patients in this trial differs from those in previous placebo-controlled trials, which is the most likely explanation for the relatively low number of vertebral fractures reported in this trial. 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 dose compared with the 30 mg dose on quality of life. Of note, the MRC Myeloma IX trial also included patients treated with high-dose chemotherapy and thus is comparable with the study population in this trial.[7]

Both daily oral clodronate and monthly intravenous pamidronate have proved substantially better than placebo for prevention of skeletal events in randomised clinical trials.[2–5] The development of more potent bisphosphonates was expected to improve the prophylactic effect on skeletal disease in patients with multiple myeloma. Zoledronic acid now seems more effective than clodronate for treatment of such patients.[7] Zoledronic acid 4 mg given as monthly infusions was also more effective than was pamidronate 90 mg in patients with breast cancer but not in patients with myeloma.[6] The reason for different effects in these two groups of patients is unknown, but it might be a result of differences in the patients' skeletal disease. The importance of osteoblast inhibition might dominate in multiple myeloma,[1,34] leading only to osteolytic lesions, whereas the mixed picture of osteosclerotic and osteolytic bone metastases in breast cancer suggests a different mechanism of bone disease.[35,36] Our results showed no significant difference between doses in the time to first skeletal event, and the curves were superimposed both for patients whose planned treatment was high-dose melphalan with stem-cell transplantation and for patients receiving regimens based on melphalan and prednisone; therefore, disease control is unlikely to have a major role in the effect of bisphosphonates. The local centralised assessment of radiographs taken at 9 months and 24 months was unfortunately incomplete and therefore less valid than was the assessment of time to first skeletal event; however, the findings were consistent with our conclusion.

In-vitro results showed an antimyeloma effect of bisphosphonates by induction of apoptosis in a dose-dependent manner. The effect was more prominent with the most potent nitrogen-containing bisphosphonates.[11] In this study, a dose-dependent effect of pamidronate on survival was not seen for the whole trial population nor for subgroups of patients according to planned treatment

(high-dose melphalan with stem-cell transplantation *vs* regimens based on melphalan and prednisone therapy). Morgan and colleagues[7] recently reported improved survival in patients with newly diagnosed myeloma treated with zoledronic acid compared with those treated with clodronate. This finding does not exclude a similar effect by pamidronate as suggested by the in-vitro studies.[11] Future studies comparing different doses of pamidronate and zoledronic acid are needed to find the best dose of bisphosphonate for both prevention of bone disease and improvement of overall survival in multiple myeloma.

The association between osteonecrosis of the jaw and bisphosphonate treatment was first recognised in about 2003. This trial was planned at an earlier time and therefore no attempts had been made to prevent this adverse effect. Although our analysis was retrospective, and risked underestimating the number of events of osteonecrosis of the jaw, we noted a cumulative risk for osteonecrosis of the jaw of about 14% in patients who continued monthly pamidronate. Two cases were reported in the 30 mg group and eight in the 90 mg group. In the recent MRC Myeloma IX trial,[7] osteonecrosis of the jaw was reported in 3·5% of patients treated with zoledronic acid compared with 0·5% treated with clodronate, but time to event was not reported. Additionally, in our study more patients in the 90 mg group discontinued treatment because of nephrotoxicity than did patients in the 30 mg group. Although these differences were not significant, they suggest that the lowest efficient dose of bisphosphonate should be used.

Our observations on nephrotoxicity support the lower effective bisphosphonate doses. Although not significant, the higher number of patients withdrawn from the trial because of increasing creatinine concentration in the 90 mg group compared with the 30 mg group suggests a higher nephrotoxicity associated with 90 mg pamidronate. Changing from 90 mg pamidronate or 4 mg zoledronic acid to 30 mg pamidronate is likely to reduce the cost of treatment.

Strengths of our study include the double-blind, placebo-controlled design, the large number of patients, and the use of a validated instrument for assessment of quality of life with a high response rate. Limitations of the study were that planned radiographs were not available for many patients and the effect of other medications could not be analysed. Additionally, analysis of osteonecrosis of the jaw was based on retrospective data.

Our results suggest that pamidronate 90 mg per month is not superior to a dose of 30 mg for prevention of skeletal events or for improvement of 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 Myeloma IX trial suggest that 4 mg zoledronic acid is superior to oral clodronate, including an improvement in survival, for treatment of patients with myeloma.[7] Currently, there are no published data that compare 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 optimum use of bisphosphonates in myeloma. However, we conclude that 30 mg pamidronate given in monthly infusions is as effective as 90 mg pamidronate and could be recommended for prevention of skeletal disease in myeloma patients.

Whether other osteoclast inhibitors such as RANKL-Ab[37] or RANK-Fc[38] can increase the effect further remains to be shown. However, complete prevention of skeletal events in patients with multiple myeloma will probably need abolition of osteoblast inhibition, for example by antibody inhibition of DKK1,[39] but no clinical data for this approach have been published.

Panel: Research in context

Systematic review

All previous phase 3 trials of pamidronate used a dose of 90 mg,[4-6] which is stated as the recommended dose in guidelines.[16] This study is the first comparison of two doses of pamidronate.

Interpretation

This study shows that pamidronate 90 mg per month is not significantly more effective than is 30 mg per month for improvement of physical function in patients with newly diagnosed multiple myeloma. Therefore, we suggest that 30 mg given once a month should be the recommended pamidronate dose for prevention of multiple myeloma bone disease to reduce cost and toxicity.

Contributors

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

See Online for webappendix

Conflicts of interest

PG has received grant support from Janssen-Cilag, a speaker's bureau from Celgene, and fee as chairman of the data monitoring committee for BioInvent. AW has received grant support from Janssen-Cilag, fees for consultancy from Janssen-Cilag and Pharmion, and payment for advisory board participation from Novartis. HH-H has received speakers fees. The Nordic Myeloma Study Group has received grant support from Janssen-Cilag, Celgene, Amgen, and Nordpharma. All other authors declared no conflicts of interest.

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