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The effects of 8-year pamidronate treatment on skeletal morbidity in patients with advanced multiple myeloma

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Background. In patients with multiple myeloma (MM) osteolytic bone destruction progresses despite a reduction of tumor mass achieved with chemotherapy. The aim of the study was to evaluate the efficacy of pamidronate, an inhibitor of osteoclastic bone resorption administered to MM patients receiving anti-myeloma chemotherapy acc. to the VMCP/VBAP alternating regimen.
Material and method. 46 patients with stage III myeloma and osteolytic lesions received either pamidronate (Aredia; Novartis) 60 mg i.v. in 4 – hour infusions monthly (n=23) or chemotherapy alone (control group n=23).
Results. On comparison of consecutive skeletal X- ray surveys performed after 6, 12, 18, 24, 30, 36, 42, 48, 54 and 66 cycles of pamidronate the progression of osteolysis was respectively found in 67%, 39%, 27%, 20%, 25%, 25%, 60%, 80%, 92% and 96% of patients. In the control group the corresponding figures were: 79%, 70%, 30%, 44%, 50%, 40%, 66% and 100% (p>0,16). Median time to the occurrence of the first skeletal-related event was 13 months in the pamidronate group and 7 months in the control group. The mean number of skeletal events (pathologic fractures, radiation or surgery of bones and spinal cord compression) per year in the first 4 years of treatment was 1.42 in the pamidronate group and 1.96 in the control group. During further treatment these values reached 0.51 vs 0.9, respectively (p=0.08). At the end of the 8 years the proportion of patients who had developed skeletal events (excluding vertebral fractures) was lower in the pamidronate group as compared to the control group – 52% vs 56%, respectively (p=0.42). The ratio of patients with vertebral pathologic fractures was identical – 76% vs 75%, but the number of vertebral fractures was lower in the pamidronate group than in the control group – 50 vs 71, respectively (1.2 vs 1.77 per year in the first 4 years p=0.07 and 0.84 vs 0.91 in the next 4 years of treatment). During the 4 latter years of study decreases of the blood hemoglobin level occurred with the same frequency among the pamidronate patients and in controls. No significant differences of patient survival were observed between the pamidronate group and the control group (median: 21 vs 20 months from randomization, p= 0.78 and median: 50 vs 45 months since MM diagnosis, p= 0.20). 5-year and 8-year survival was 48% and 30%, respectively, for patients receiving pamidronate, as compared to 17% and 13%, respectively for patients receiving chemotherapy only.
Conclusions. Long-term pamidronate treatment moderately reduces myeloma-related skeletal morbidity. As the treatment duration lengthens the effect of pamidronate on skeletal morbidity becomes less pronounced and the difference in the incidence of anaemia between the pamidronate group and the controls is much less distinct.

Wpływ 8-letniego leczenia pamidronianem powikłań kostnych w zaawansowanym szpiczaku plazmocytowym

Cel. U chorych na szpiczaka plazmocytowego (sz.p.) mimo redukcji masy nowotworowej pod wpływem chemioterapii destrukcja osteolityczna często postępuje. Celem pracy była ocena skuteczności pamidronianu, inhibitora osteoklastycznej resorpcji kostnej u chorych na sz.p. z osteolizą, w III okresie choroby.
Materiał i metody. 46 chorych otrzymujących chemioterapię przeciwnowotworową VMCP/VBAP randomizowano: 23 włączono do leczenia pamidronianem (Aredia) 60 mg i.v. comiesięcznie, także 23 chorych, stanowiących grupę kontrolną, pozostawiono wyłącznie na chemioterapii.
Wyniki. W badaniu radiologicznym kośćca przeprowadzonym po 6, 12, 18, 24, 30, 36, 42, 48, 54 i 66 cyklach pamidronianu, porównując obraz każdego kolejnego badania z poprzednim, progresję osteolizy stwierdzono odpowiednio u: 67%, 39%, 27%, 20%, 25%, 25%, 60%, 80%, 92% i 96% chorych. W grupie kontrolnej progresja osteolizy wystąpiła odpowiednio u: 79%, 70%, 30%, 44%, 50%, 40%, 66% i 100% chorych (p>0,16). Mediana czasu do wystąpienia pierwszego powikłania kostnego wynosiła w grupie leczonej pamidronianem 13 miesięcy, a w grupie kontrolnej 7 miesięcy. Średnia liczba powikłań kostnych na rok była mniejsza w grupie leczonej pamidronianem (w pierwszych 4 latach leczenia 1,42 vs 1,96, w późniejszych

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latach 0,51 vs 0,9; p=0,08). Pod koniec 8-letnich badań łączny odsetek chorych, u których wystąpiły powikłania kostne, nie różnił się w obu grupach (52% vs 56%; p= 0,42). Odsetek chorych z patologicznymi złamaniami kręgów był identyczny w obu grupach 76% vs 75%, natomiast liczba złamań kręgów była mniejsza w grupie pamidronianowej, wynosząc odpowiednio 50 vs 71 (1,2 vs 1,77 na rok w pierwszych 4 latach, p=0,07 i 0,84 vs 0,91 w późniejszych latach). W ciągu ostatnich 4 lat badań niedokrwistość występowała z taką samą częstotliwością u chorych leczonych pamidronianem co w grupie kontrolnej. W grupie pamidronianowej mediana przeżycia wynosi 21 miesięcy od randomizacji i 50 miesięcy od rozpoznania sz.p., a w grupie kontrolnej 20 miesięcy od randomizacji i 45 miesięcy od rozpoznania sz.p. (p=0,78; p=0,20). W grupie pamidronianowej 5 i 8-letnie przeżycia wynosiły odpowiednio 48% i 30%, a w grupie kontrolnej odpowiednio 17% i 13%.
W n i o s k i. Długotrwałe leczenie pamidronianem umiarkowanie łagodzi szpiczakową chorobę kości. W miarę wydłużania leczenia wpływ pamidronianu na chorobę kości staje się mniej wyraźny, a niedokrwistość występuje podobnie często jak w grupie kontrolnej.

Key words: multiple myeloma, osteolytic lesions, pamidronate, bisphosphonates
Słowa kluczowe: szpiczak plazmocytowy, osteoliza, pamidronian, bisfosfoniany

Introduction

Multiple myeloma is characterized by the accumulation of malignant plasma cells in the bone marrow and by osteolytic bone destruction, which is responsible for increased morbidity and mortality. Skeletal destruction results from increased osteoclastic activity, which is not accompanied by a comparable increase in bone formation and is mediated by cytokines, which are produced locally in the bone marrow microenvironment by either myeloma cells or stromal cells. The interaction of plasma cells with stromal cells in the bone marrow microenvironment is crucial for the activation of osteoclasts [1]. Apart from cytokines, such as interleukin-6 (IL-6), IL-1β, IL-11 and the tumour necrosis factors (TNFs), which are known to have osteoclast activating properties, the identification of new molecules, such as the receptor activator of nuclear factor-kappa β (RANK), its ligand (RANKL), osteoprotegerin (OPG; the decoy receptor of RANKL), macrophage inflammatory protein-1 alpha (MIP-1α) and vascular endothelial growth factor (VEGF) has provided new insight into the pathogenesis of multiple myeloma bone disease. Inhibition of OPG production by myeloma cells associated with increased expression of RANKL in the bone marrow disrupt RANKL/OPG ratio in favor of the osteoclastogenic factor RANKL. The main role of the RANKL/OPG axis deregulation in multiple myeloma–induced osteolysis is highlighted by the high potency of RANKL inhibitors such as OPG or RANK-Fc to prevent both excessive osteoclast development and lytic bone lesion appearance in different murine myeloma models [2]. VEGF is a multifunctional cytokine that plays a role in angiogenesis and tumour neovascularization, and has recently been implicated as a mediator of osteoclastogenesis in multiple myeloma. VEGF is expressed by myeloma cells and it binds to the receptor, VEGFR-1, that is predominantly expressed on osteoclasts. VEGF directly enhances osteoclastic bone resorption and survival of mature osteoclasts [3].

In multiple myeloma patients new bone formation is reduced and bone lesions usually do not heal even in patients with complete remission of the proliferative process. This suggests that a functional defect of osteoblasts is also important in the lytic process. Indeed, the number and function of osteoblasts are decreased in myeloma with osteolytic lesions. Recently Tian et al. [4] have reported the production of the potential osteoblast inhibitor DKK1 by myeloma cells. Actually, DKK1 can block Wnt signaling, an important pathway involved in osteoblast differentiation and function, and its overexpression in multiple myeloma is associated with lytic bone disease.

Bisphosphonates inhibit osteoclastic bone resorption by inhibiting osteoclastic recruitment and maturation, inducing osteoclast apoptosis, and interrupting their attachment to the bone. They also induce apoptosis of human multiple myeloma cells, [5] reduce IL-6 secretion by bone marrow stromal cells, and cause expansion of γδ T-cells with anti-multiple myeloma activity, suggesting a possible anti-myeloma effect of these agents [6]. It has been reported that pamidronate has either direct or indirect anti-tumour effect in patients with multiple myeloma [7]. Interestingly, it has been recently shown that both pamidronate and zoledronic acid stimulate OPG production by primary human osteoblasts [8].

The second-generation aminobisphosphonate, pamidronate, has been shown to reduce skeletal events, including pathologic fractures [9, 10] and to decrease bone resorption markers in multiple myeloma patients [11, 12].

In the Warsaw Institute of Haematology and Blood Transfusion the efficacy of pamidronate was being evaluated in multiple myeloma patients since October 1995. The results of the first twenty once-monthly cycles of pamidronate demonstrated its effectiveness in the prevention and treatment of hypercalcaemia, hypercalciuria and bone pain [13, 14]. The results obtained during a median 48 month pamidronate treatment were presented at the 28th World Congress of the International Society of Hematology, at the 6th Annual Meeting of the European Haematology Association and at the XX Congress of the Polish Society of Haematology and Blood Transfusion [15] and are the subject of this paper.

Table I. Clinical characteristics of patients at entry into the pamidronate study

Parameter		Pamidronate	Control
Sex M/F	no. of patients	10 / 13	16 / 7
Age (yr) x ± SD		60 ± 10	66 ± 9
M- protein IgG/ IgA/ BJ/NS	no. of patients	16 / 7 / 0 / 0	17 / 3 / 2 / 1
Stage D.S. II/ III	no. of patients	0 / 23	1 / 22
Osteolysis	no. of patients (%)	4 (17)	5 (21)
Vertebral fractures		2 (9)	2 (9)
Osteolysis + vertebral fractures		17 (74)	16 (70)
Hypercalcaemia >2.75 mmol/l	no. of patients	5	2
Urine Ca/creat. ratio >0.3 mmol/l	no. of patients	9	5
Serum creatinine <176 μmol/l	no. of patients	23	23
Bone pain score	no. of patients (%)		
1-2		13 (57)	15 (65)
3-4		10 (43)	8 (35)
ECOG performance score	no. of patients (%)		
1 or 2		14 (65)	17 (74)
3 or 4		9 (35)	6 (26)
Time since MM diagnosis	no. of patients (%)		
<1 year		9 (39)	11 (48)
>1 year		14 (61)	12 (52)
Time since start of VMCP/VBAP therapy	(mo)		
– median		24	19
– mean		26 ± 22	26 ± 33

Material and method

The study included 46 patients with multiple myeloma and osteolysis hospitalised every month at the Department of Haematology of the Institute of Haematology and Blood Transfusion in Warsaw. Patient characteristics are presented in the Table I. All patients received anti-myeloma chemotherapy according to the VMCP/VBAP alternating regimen scheduled at 4 – week intervals. The patients were randomised to receive either pamidronate (Aredia; Novartis) 60 mg *i.v.* in a 4-hour infusion monthly (n=23) or chemotherapy alone (control group n=23). Treatment with pamidronate was continued indefinitely.

The following parameters were estimated in each patient at the trial entry and then at one-month intervals during each hospitalization of the patient: performance status using a 4-point scale (1 – normal, 2 – light work possible, 3 – up and about >50% of the day, 4 – confined to bed), pain frequency and pain severity using a 5-point scale (1 – none, 2 – mild, 3 – moderate, 4 – severe, 5 – intolerable), analgesic drug use (1 – none, 2 – simple analgesic or NSAID, 3 – moderate analgesic, 4 – opiates) [16], total and ionized serum calcium concentrations as well as 24 – hour urine and two-hour fasting urine samples for the excretion of calcium (the latter was expressed as ratio to urinary creatinine and was measured during the first 24 months of study). For comparative reasons fasting urinary calcium and creatinine excretion were also determined in 11 healthy persons. Hypercalcaemia was defined as albumin adjusted serum calcium of >2.75 mmol/l. A complete X-ray skeletal survey including long bone imaging was conducted at the entry point and then every six months and was evaluated by a radiologist who was blinded as to the treatment assignments. Assessment of X-ray images was always performed by the same radiologist. Progression of radiological changes was assessed on the basis of either occurrence of new osteolytic foci or increase in size of previously revealed changes. Comparison of size of osteolytic foci included their direct measurement. X-ray survey was always performed using the same X-ray equipment and the same films.

Changes from baseline in bone pain scores for analgesic drug use, performance status scores, differences in calcium concentrations and differences in Kaplan-Meier survival curves were analyzed by Wilcoxon's rank test. The number of patients with skeletal complications and the number of complications were compared by the Chi square test and Fisher's exact test.

Results

All 46 patients included in this study were followed up until death or for at least 6 years, except for 2 patients who were lost to follow up at 7 months and 3 years, respectively.

As it was illustrated in our previous publication during the first months of treatment pain reduction was greater in the pamidronate group than in the control group ($p<0.05$). Beginning from the 9th month of observation there were no differences in pain scores between the compared groups [14].

During the study mean serum calcium concentrations remained within the range of normal values in the pamidronate group (Table II).

Hypercalcaemia was observed in 6 patients at entry point. In 5 of these patients pamidronate restored and maintained normocalcaemia for a median of 6 months. In 3 patients aggressive plasma cell proliferation was accompanied by reoccurrence of hypercalcaemia. The incidence of hypercalcaemia episodes was lower in the group of patients treated with pamidronate, as compared to the control group, however the difference did not reach statistical significance. 24-hour urinary calcium excretion was increased (>6.25 mmol/24h) at the entry point in 8 patients in the pamidronate group. During pamidronate treatment the value of this parameter returned to normal in 6 patients, remained increased in 2 and was increased

Table II. Calcium concentration in serum and urine at study onset and after 21 and 36 months (mo) of study

	Baseline	21 mo	36 mo
Albumin adjusted serum calcium (mmol/l)			
x ± SD			
pamidronate	2.55 ± 0.22	2.21 ± 0.25	2.15 ± 0.23
control	2.43 ± 0.19	2.30 ± 0.28	2.22 ± 0.25
Urinary calcium excretion (mmol/24h)			
x ± SD			
pamidronate	4.01 ± 3.10	5.11 ± 2.90	
control	5.27 ± 1.90	5.18 ± 2.00	
healthy persons, range	2.50 – 6.25		
Urinary calcium excretion mmol/ mmol urine creatinine			
x ± SD (range)			
pamidronate	0.61 ± 0.52	0.31 ± 0.28	
control	0.41 ± 0.59	0.33 ± 0.38	
healthy persons	0.11 ± 0.08 (0.03 – 0.30)		

along with observed progression of disease in 2 patients. Elevated values (>0.3) of urine Ca/creat ratios in 9 patients returned to normal during pamidronate treatment; the Ca/creat. ratio was elevated in 1 patient, normal in 8 patients before and during treatment, while in 5 patients the ratio values varied. In the control group the Ca/creat. ratio varied, however in most cases it exceeded 0.3.

Skeletal X-ray examination was performed after 6, 12, 18, 24, 30, 36, 42, 48, 54 and 66 cycles of pamidronate – by comparing each consecutive imaging with the previous one the progression of osteolysis was found in 67%, 39%, 27%, 20%, 25%, 25%, 60%, 80%, 92%, and 96% of patients respectively. In the control group the corresponding ratios were 79%, 70%, 30%, 44%, 50%, 40%, 66% and 100% (p>0.16) (Table III).

Table III. Occurrence of progression of osteolysis* by the end of cycle 6, 12, 18, 24, 30, 36, 42, 48, 54 and 66 of pamidronate treatment

	% of MM patients with progression of osteolysis		
	pamidronate	control	
6 cycles	67	79	
12 cycles	39	70	
18 cycles	27	30	
24 cycles	20	44	
30 cycles	25	50	p>0.16
36 cycles	25	40	
42 cycles	60	66	
48 cycles	80	100	
54 cycles	92	N.D.	
66 cycles	96	N.D.	

* evaluated by comparing each consecutive skeletal X-ray imaging with previous one
N.D. – not done

The mean number of skeletal events (pathologic fracture, radiation or surgery to bone and spinal cord compression) per year during the first 4 years of treatment was 1.42 in the pamidronate group and 1.96 in the control group, while during further treatment it was found to be 0.51 vs 0.9, respectively (p=0.08) (Figure 1).

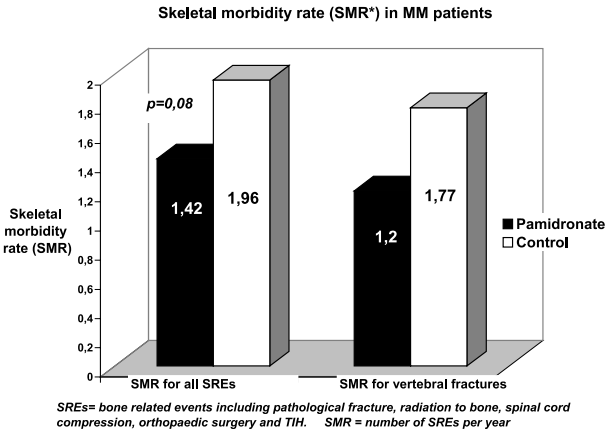

Figure 1. Number of bone related events including pathological fracture, radiation to bone, spinal cord compression, orthopaedic surgery and tumour induced hipercalcaemia per year in the pamidronate group and the control group of multiple myeloma patients after 48 cycles of therapy

During the whole period of our study bone irradiation was performed in 4 patients from the pamidronate group and in 2 patients from the control group.

Median time to the first skeletal-related event was 13 months in the pamidronate group and 7 months in the control group.

During the entire study period the proportion of patients who developed skeletal events (excluding vertebral fractures) was slightly lower in the pamidronate group than in the control group – 52% vs 56% (p=0.42) (Figure 2).

The ratios of patients with pathologic vertebral fractures were similar – 76% vs 75%, respectively, but the number of vertebral fractures was lower in the pamidronate group, 50 vs 71 (1.2 vs 1.77 per year in the first 4 years and 0.84 vs 0.91 in the next years of treatment; p=0.07) (Figure 1).

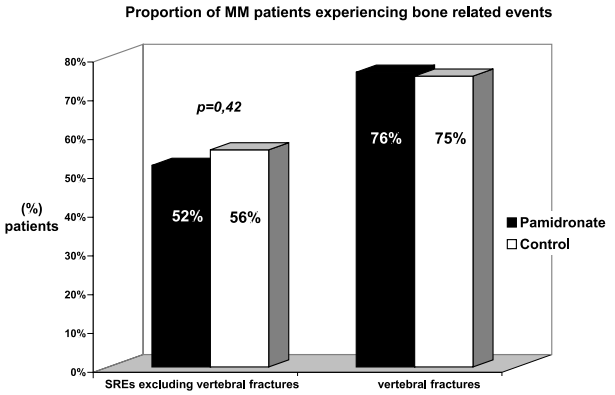

Figure 2. Proportion of multiple myeloma patients experiencing bone related events in the pamidronate group and the control group during the entire study period

In one patient treated with pamidronate we observed "reconstruction" of pathologically fractured cervical vertebrae after irradiation.

During the first 24 months of study decreases in blood haemoglobin concentration were more frequent in the pamidronate group than in the control group (72% vs 41%, respectively) and mostly were accompanied by progression of proliferation. (Table IV).

Table IV. Occurrence of anaemia in multiple myeloma patients during long-term pamidronate treatment

	Proportion of patients with Hb concentration <8.0 g/dl		
	pamidronate	control	p
After 21 cycles	72%	41%	0.04
After 36 cycles	72%	50%	0.23
After 53 cycles	40%	65%	0.18
Up to 66 cycles	60%	65%	0.49

The Kaplan- Meier survival curves did not differ in the two studied groups (Figures 3, 4). Median survival time from randomization was 21 months in the pamidronate group and 20 months in the control group, p=0.78 (Figure 3). Median survival time from multiple myeloma diagnosis was 50 months in the pamidronate group and 45 months in the control group, p=0.20. The proportions of 5 and 8-year survival were 48% and 30%, respectively, for those randomized to pamidronate, as compared with 17% and 13%, respectively, in the chemotherapy-only arm (Figure 4).

At the time of analysis 3 (12%) patients in the pamidronate group and none in the control group remained alive. In the pamidronate group 18 deaths (95%) were considered to be myeloma-related while the remaining one case was caused by cardiac disease. In the control group 19 (86%) of the deaths were considered to be myeloma-related. The causes of death of the remaining 3 control patients included 1 from cerebrovascular incident, 1 from cardiac disease and 1 from infection and diabetes.

Table V. Survival of multiple myeloma patients treated with pamidronate

	Pamidronate		Control
Median survival time since randomization (months)	21	p=0.78	20
Median survival time since MM diagnosis (months)	50	p=0.20	45
% of patients who died (to March 2004)	87		100

Discussion

During the last decade the effect of treatment of osteolytic myeloma–induced bone disease with bisphosphonates was assessed in several studies [9, 10, 12, 16-24]. The core phase of the published clinical trials on pamidronate efficacy in the treatment of myeloma bone disease was confined to administration of the analyzed drug over a period from several to 12 months, whereas the extension phase (lasting till 24 months) mainly referred to the assessment of patient survival time. The trial reported here is the longest study of this kind performed on myeloma patients in whom pamidro-

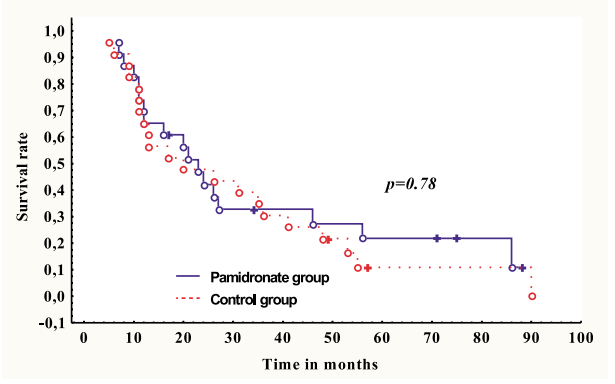

Figure 3. Kaplan-Meier estimates of survival from randomization in the study patients

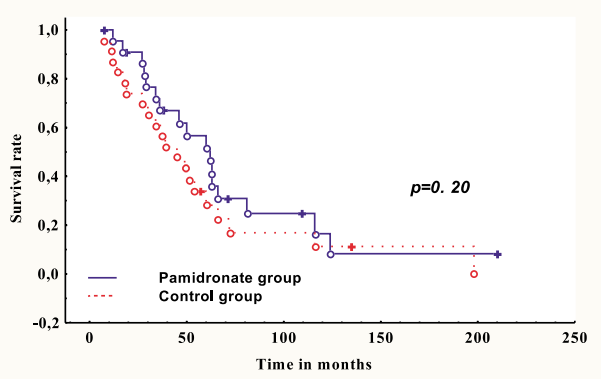

Figure 4. Kaplan-Meier estimates of survival from multiple myeloma diagnosis in the study patients

nate treatment efficacy was assessed over a period of 8 years.

Our study on pamidronate (Aredia) at a dose of 60 mg i.v. administered every month as adjuvant myeloma treatment commenced in 1995. In studies published before its onset and devoted to the effect of the drug on osteolytic bone disease pamidronate was administered at a dose not exceeding 60 mg i.v. every month and only in severe hypercalcaemia at a dose of 90 mg [25-27]. At that time such a dose was suggested by the manufacturer. More recent studies, which formed the base for pamidronate (Aredia) registration by the FDA in the US as an adjuvant treatment of osteolytic bone disease recommended its administration at a dose of 90 mg every month [9].

As it was shown in our previous study [13, 14] and also, to a certain extent, presented in this paper, in patients receiving pamidronate we observed bone pain reduction and an improvement of bone turnover indices. However, the reduction of clinical symptoms related to bone destruction was greater in patients treated with pamidronate as compared to the control group only in the first 8 months of treatment. Pamidronate administration was associated with an insignificant decrease in the proportion of patients with hypercalcaemia, but the mean serum calcium concentration remained in the normal limits during the entire study time (Table II).

Despite the administration of combined treatment, i.e. chemotherapy and pamidronate, the frequency of osteolysis progression reached 67% during the first six months of treatment. The beneficial effect of pamidronate on bone pathology became evident after twelve months of treatment as a lower rate of patients with further osteolysis progression (39% of patients in the pamidronate group *versus* 70% in the control group) as well as by a lower skeletal morbidity rate (SMR) = skeletal related events per year (1.82 *versus* 2.72) and the proportion of patients who developed a skeletal event (34% vs 52%) [14]. Median time to the first skeletal-related event was 13 months in the pamidronate group and 7 months in the control group. No differences were found in the frequency of osteolysis progression between the two groups after 24 cycles of therapy ($p>0.16$) (Table III). In the two further consecutive years of the trial the difference in the incidence of bone complications between the two groups diminished (SMR for the pamidronate group – 1.42; for the control group – 1.96) but it remained apparent over the next years; the SMRs for extravertebral complications amounted to 0.51 and 0.91 respectively. By the end of the 8-year study period the combined proportions of patients experiencing bone complications were similar in the pamidronate group and in the control group: 52% vs 58% for extravertebral complications and 76% vs 75% for vertebral fractures. A significant survival advantage has not been shown (Figures 3, 4, Table V).

The outcomes of pamidronate efficacy in multiple myeloma in respect to incidence of skeletal events and bone pain achieved in our first 21-month-study are nearly convergent with those from Berenson' s et al. trial [9, 10] so far the largest study on intravenous pamidronate effectiveness in myelomatosis.

In the study of Berenson et al. [9] 392 stage III multiple myeloma patients with osteolysis were randomized to receive either pamidronate at a dose of 90 mg or placebo, both in 4 – hour intravenous infusions administered every four weeks and combined with anti-tumor chemotherapy. Results presented in 1996, after the administration of 9 cycles, showed a remarkable decrease in the ratio of patients experiencing bone fractures and requiring orthopedic-surgical management and radiotherapy in the pamidronate group (24% vs 41%), as well as a significant decrease in the ratio of patients with hypercalcaemia episodes during the first three months of treatment (1% vs 5%). Pamidronate treatment provided significant improvement of bone pain, decreases in anti-analgesic drugs consumption and improvement of the quality of life. In 150 patients the treatment with pamidronate was continued and 41% of them received 21 cycles of therapy, after which the authors observed a decrease both in the proportion of patients experiencing various bone complications and in the number of bone complications. Among all the 392 patients no differences were found in overall survival between the pamidronate and placebo group, whereas the median survival of patients enrolled into the study during second – or greater – line chemotherapy programs was 21 months for patients receiving pamidronate and 14 months for patients receiving placebo.

It is noteworthy that in another large trial – 167 enrolled patients with Durie-Salmon stage III multiple myeloma and osteolysis treated with 90 mg of pamidronate via intravenous infusion every 3 to 4 weeks for 12 months, 49% of patients experienced at least one skeletal related event, SMR was 1.43 and the median time to the first skeletal related event was 363 days from study entry [17]. The authors have offered a possible explanation for the larger proportion of myeloma patients with a skeletal related event, as compared to the figures in the previously reported pamidronate studies – myeloma patients in this trial [17] were enrolled much earlier after diagnosis than those in the previous trials (3 months, as compared to 15 months) [9, 10]. Clinical experience shows that patients newly diagnosed with multiple myeloma go through a period of increased risk of fracture until their primary chemotherapy begins to take effect.

A large, international, randomized trial designed to directly compare the efficacy and safety of 4 or 8 mg of zoledronic acid with 90 mg of pamidronate has shown that pamidronate was as effective as zoledronic acid in reducing the risk of skeletal complications in multiple myeloma patients with osteolysis [17-20].

Terpos et al. [12] have compared the effect of pamidronate (90 mg) and ibandronate (4 mg) in monthly intravenous infusions on bone remodelling and disease activity in multiple myeloma. In both groups the combination of chemotherapy with either pamidronate or ibandronate produced a reduction in bone resorption and tumour burden. However, they observed a greater

reduction in serum concentration of biochemical markers of bone resorption (NTX, TRACP-5b), IL-6 and beta$_2$-microglobulin in the pamidronate group than in the ibandronate group. There was no difference in the occurrence of skeletal events during the 10 months of follow-up. On the other hand a recent randomized, double blind, placebo controlled trial failed to show any effect of 2.0 mg of ibandronate on bone morbidity reduction or on prolongation of survival in multiple myeloma [21].

In the Brincker et al. [22] trial, 304 multiple myeloma patients were randomised to receive either oral pamidronate at a dose of 300 mg/d. or placebo, in addition to conventional treatment. It was found that pamidronate showed no effect on skeletal morbidity. The negative result of this study was attributed to the very low absorption of orally administered bisphosphonates.

The Medical Research Council (VIth Myeloma Study) in the UK has performed the largest trial on clodronate in multiple myeloma [23]. In addition to chemotherapy (acc. to ABCM, ABCMP), 536 newly diagnosed patients were randomised to receive either oral clodronate (1600 mg/d) or placebo. After one year of follow-up, the percentage of non-vertebral fractures was 13.2% in the placebo group and 6.8% in the clodronate group ($p=0.036$). Vertebral fractures were also less frequent in the clodronate group, than in the placebo group (38% vs 55%; $p<0.001$). At 2 years, the patients who received clodronate had a better performance status and experienced lesser back pain than those treated with placebo. Although there was no difference in overall survival between the two groups (34 months vs 36 months), in the subgroup of 153 patients with no skeletal fractures at presentation there was observed a significant survival advantage ($p=0.006$) in favour of 73 patients receiving clodronate; median survivals were, respectively, 59 months and 37 months, and proportions of 5-year survivals – 46% and 35% (24).

We would like to stress the appearance of reconstruction of vertebrae destroyed by the osteolytic process in one patient on supportive treatment with pamidronate and irradiation [28]. Regeneration of bone lesions in multiple myeloma is extremely unusual – perhaps bisphosphonates may promote the occurrence of this phenomenon [20].

A previously published report included the early adverse events of pamidronate administration [13]. In our further studies on the assessment of long-term pamidronate treatment attention was drawn to the more frequent occurrence of anaemia in the pamidronate group than in the control group (72% vs 41% after 21 cycles of pamidronate) [14]. A higher incidence of anaemia in patients treated with pamidronate was also observed by Berenson et al. [10]. Although the reason for such a phenomenon remains unclear it should be stressed that the appearance of anaemia in our patients was usually associated with proliferation progression and in the later period of treatment the difference in incidence of anaemia between pamidronate group and controls tended to disappear (Table IV).

Bisphosphonates are widely administered in the management of myeloma-associated hypercalcaemia, however their exact clinical role in multiple myeloma remains unclear. In order to summarize the available knowledge concerning advantages and disadvantages of bisphosphonate application in multiple myeloma the Cochrane Myeloma Review Group performed a meta-analysis based on 11 trials that included 2183 assessable patients: 1113 patients treated with bisphosphonates and 1070 controls. The meta-analysis demonstrated a beneficial effect of both intravenous pamidronate and clodronate on the prevention of pathological vertebral fractures ($p=0.0003$), on the prevention of hypercalcaemia ($p=0.0001$), and on the experienced pain, ($p=0.0001$). The analysis of bisphosphonate effect on pain was based on clinically heterogenous data and must be interpreted with caution. In the absolute terms, the results may be interpreted as follows: 10 patients with multiple myeloma should be treated to prevent one vertebral fracture, 19 to prevent one patient from developing hypercalcaemia and 7 to prevent one patient from experiencing pain [29, 30].

The American Society of Clinical Oncology convened an Expert Multidisciplinary Panel under the auspices of its Health Services Research Committee to develop recommendations regarding the use of bisphosphonates for multiple myeloma. The Panel reviewed pertinent information from the published literature through January 2002 and concluded: Bisphosphonates provide a meaningful supportive benefit to multiple myeloma patients with lytic bone disease. However, further research on bisphosphonates should answer the following questions: 1) when to start and stop therapy, 2) how to integrate their use with other treatments for lytic bone disease, 3) how to evaluate their role in myeloma patients without lytic bone involvement, 4) how to distinguish between symptomatic and asymptomatic bone events, and 5) how to better determine their cost – benefit consequence [31].

Conclusions

Long-term monthly intravenous pamidronate administration as an adjunct to chemotherapy in patients with advanced multiple myeloma and osteolysis moderately reduces skeletal morbidity, but does not significantly prolong survival. When treatment duration is extended the effect of pamidronate on skeletal morbidity becomes less pronounced and the difference in the incidence of anaemia between the pamidronate group and the control group tends to disappear.

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