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Original article

Intravenous neridronate for skeletal damage treatment in patients with multiple myeloma

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Abstract. Almost 70-80% of the patients with Multiple Myeloma (MM) in advancer phase, of the disease show osteolytic lesions and/or pathologic fractures, with or without secondary osteoporosis. An accelerated osteoclast-mediated bone absorption is believed to be the main cause of bone damage in MM. Osteoclast can be activated by a variety of microenvironmental factors. Bisphosphonates (BF) induce the apoptosis of osteoclasts and inhibit osteoclastogenesis, thus preventing bone absorption. As well as BFs, the so-called second-generation BF (N-BF) may impair the activity of osteoclast. Neridronic acid (NER) is a N-BF molecule officially registered for the treatment of osteogenesis imperfecta. Nevertheless, NER has shown a remarkable efficacy in Paget's disease, postmenopausal osteoporosis and, most recently, in androgen deprivation-treated prostatic carcinoma. The primary endpoint of this study was to evaluate hip and spine Bone Mineral Density (BMD) modifications over the 12-month treatment with NER in a group of patients affected by MM with evidence of initial skeletal damage. Secondary endpoints were (1) changes of calcium and total Alkaline Phosphatase (tAP) plasma levels during treatment with NER and (2) tolerability of 100 mg NER monthly administration for 12 months. These data suggest that NER, if administered at these doses and timing, might allow at least for one year sustained BMD increases in patients . NER has been highly tolerated in this study. The almost complete absence of adverse effects has prompted us to reduce the time of infusions at the end of the study. In conclusion, this study provides the first data on the efficacy and safety of NER in patients with MM-induced bone damage. These initial data encourage wider phase III trials to clearly assess its efficacy in preventing skeletal-related events and its possible anti-neoplastic properties. (www.actabiomedica.it)

Key words: Skeletal damage, osteoporosis, multiple myeloma, neridronate, bisphosphonates

Introduction

The 70-80% of the patients with Multiple Myeloma (MM) in advanced phase of the disease show osteolytic lesions and/or pathologic fractures, with or without secondary osteoporosis (1). Skeletal damage might be associated with hardly treatable pain and various neurological signs (such as peripheral neuropathy and paraplegia) caused by nerve root compression. An early and effective treatment of MM-induced bone destruction is therefore needed to prevent the occurrence of a substantial quality of life deterioration in MM-affected individuals, whose median survival at present does not presently exceed 60 months.

An accelerated osteoclast-mediated (2-4) bone absorption is believed to be the main cause of bone damage in MM. Osteoclast can be activated by a variety of microenvironmental factors (5-7). Bisphosphonates (BF) induce the apoptosis of osteoclasts and inhibit osteoclastogenesis, thus preventing bone absorption. As well as BFs, the so-called second-generation BF (N-BF) may impair the activity of osteoclast. In addition, they possess both direct and indirect anti-neoplastic properties, some of which have been demonstrated for the Zoledronic acid (ZOL) in *in-vivo* experimental models (8-11). The treatment of choice for MM-induced bone damage is at present a monthly 4 mg ZOL intravenous administration.

Neridronic acid (NER) is a N-BF molecule officially registered for the treatment of *osteogenesis imperfecta* (12). Nevertheless, NER has shown a remarkable efficacy in Paget's disease (13), postmenopausal osteoporosis (14) and, most recently, in androgen deprivation-treated prostatic carcinoma (15).

To our knowledge, no study has evaluated NER in MM-induced bone destruction.

Patients and methods

Between June 2002 and June 2003 seven subjects (5 males and 2 females, aged from 53 to 72 years) with IgG (5), IgA (1), and light chain (1) MM have been selected. The disease stages at diagnosis were as follows: IA (1), IIA (2), IIIA (3), IIIB (1). At enrollment, all patients had evidences of skeletal lytic lesions/pathologic fractures shown by plain radiography or secondary osteopenia (-2,5 S.D. <T-Score <-1 S.D.)/osteoporosis (T-Score <-2,5 S.D.), demonstrated by Dual Energy X-ray Absorptiometry (DEXA), or both, without any concomitant skeletal metabolic disease (Tab. 1). All patients showed an ECOG Performance Status score ≤2. No patients had creatinine and total bilirubin plasma levels ≥3 mg/dL or ≥2.5 mg/dL respectively. Double autologous haematopoietic stem cell or bone marrow trasplantation after one or more chemotherapy-based induction regimens had been performed in all patients. None of them received oral Calcium or Vitamin D supplements during the study. No patient had been previously treated with ZOL. A written informed consent has been obtained from any patient before the enrollment.

Patients received an intravenous, 0.9% saline diluted solution, 100mg monthly NER administration for 12 months. Each infusion had a duration of 150 mins. DEXA (Hologic QDR-4500 A, *Hologic Inc.*, Bedford, MA, USA) was used to measure hip and lumbar spine (L1-L3) Bone Mineral Density (BMD) at enrollment, after 6 and 12 months. MM has been monitored through standard monthly plasma and urinary tests and, with frequency dependent on the single patients, bone marrow plasma cell percentage modifications. In addition, monthly total Alkaline Phosphatase (tAP) plasma levels have been obtained.

The primary endpoint of this study was to evaluate hip and spine BMD modifications over the 12-month treatment with NER, as described above. Secondary endpoints were (1) changes of calcium and tAP plasma levels during treatment with NER and (2) tolerability of 100 mg NER monthly administration for 12 months.

Results

1. Treatment efficacy

Bone mineral density. Lumbar spine mean BMD change (± SD) versus baseline was, respectively, 1.3% and 3.5% six and twelve months after the first dose of

Table 1. Patient data

Patient number	Age	Weight	BMI	Sex	Yrs since menopause	Yrs from MM diagnosis	MM type	MM clinical stage at diagnosis	Osteolysis/ Fractures/ Osteopenia at enrollment
I	64	82	28.4	M		7	IgG, pr	IIIA	Yes/Yes /No
II	62	82	25.3	M		3	IgG, pr	IIA	Yes /No/No
III	54	74	25.6	M		3	IgA, cr	IIIA	No/No/ Yes
IV	72	54	21.1	F	22	2	IgG, pd	IA	Yes /No/ Yes
V	56	82	25.3	M		1	IgG, pr	IIA	Yes /No/ Yes
VI	62	65	23.9	F	12	2	IgG, pr	IIIA	No/No/ Yes
VII	53	70	25.7	M		2	LC, pr	IIIB	Yes/Yes/Yes
Average	60.4	72.7	25						
SD	6.7	10.6	2.2						

Abbreviations: BMD: Bone Mineral Density; cr: complete remission; pr: partila remission; mr: minimal remission; pd: disease progression, LC: Light Chains

Table 2. Mean baseline, 6-month and 12-month Lumbar Spine and Hip BMD % change

Skeletal area	BMD (g/cm²) Average (SD), Baseline	6-month BMD % change Vs Baseline	12-month BMD % change Vs Baseline	Skeletal area	BMD (g/cm²) Average (SD), Baseline	6-month BMD % change Vs Baseline	12-month BMD % change Vs Baseline
Spine (L1-L3)	0.90 (0.14)	1.3	3.5	NER Femore	0.84 (0.18)	2.8	1.4

NER. Hip mean BMD change (± SD) versus baseline was, respectively, 2.8% and 1.4% six and twelve months after the first dose of NER (Tab. 2). Mean BMD changes never fell below baseline values (Fig. 1).

Calcium. No significant change of mean calcium plasma levels has been observed during the treatment (Fig. 2). In fact, as shown in Fig. 2, at six and at twelve months from the beginning of the treatment, calcium plasma levels were substantially comparable to baseline levels. No malignant hypercalcemia event has been observed during the study.

Total Alkaline Phosphatase. Starting from three months since the beginning of NER administration, mean tAF plasma levels have progressively decreased. After ten months, mean tAF levels were reduced by more than 50% with respect to the baseline values (Fig. 3).

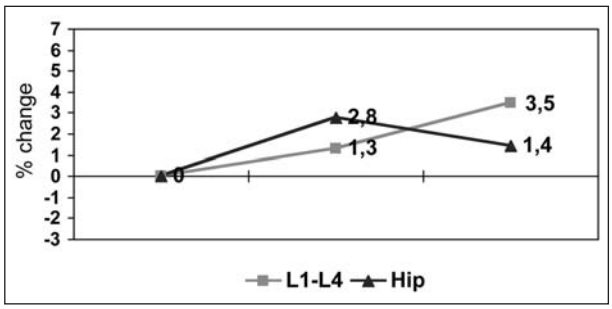

Figure 1. Lumbare spine (L1-L4) and Hip BMD, mean % change

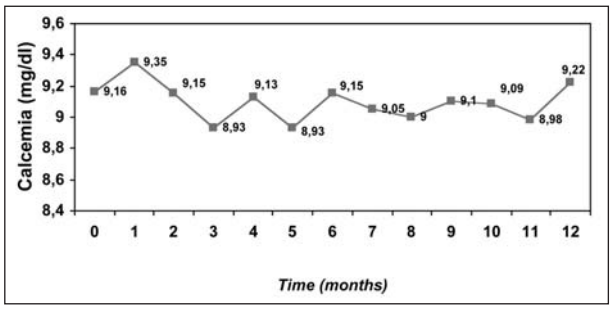

Figure 2. Calcium plasma levels

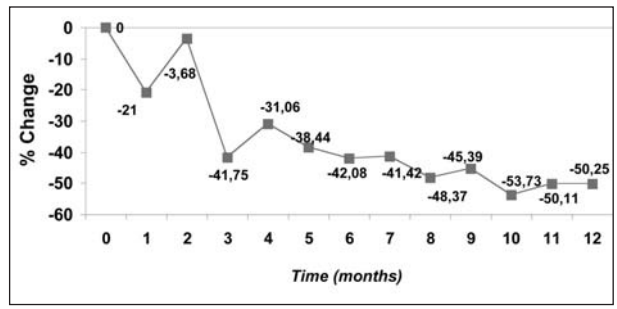

Figure 3. Total Alkaline Phosphatase plasma levels, mean % change

2. Treatment safety

Every single infusion has been constantly monitored by trained personnel. Starting from the second infusion, patients have been monthly interviewed in order to collect data on possible treatment-related adverse events occurring at home. Creatinine, urea nitrogen, potassium and sodium plasma levels have been monthly measured. Three flu-like syndromes with fever ≤ 38°C and muscle pain have occurred in different patients within 36 hours after the end of NER infusion. All these events promptly resolved after NSAID administration.

Discussion

Although BMD changes have limited value in assessing the efficacy of BFs in MM, this technique provides fundamental data to assess skeletal damage progression in patients with MM and secondary osteopenia or osteoporosis but no lytic lesions or pathologic fractures at diagnosis or at later stages of disease. Moreover, the number of skeletal-related

events (SRE) e.g. pathologic fractures, vertebral compressions with fracture, surgery to treat or prevent fractures, radiation therapy for the treatment of bone pain, occurring in a phase II study including a small group of patients would probably be too little to satisfactorily assess the efficacy of a BF molecule in preventing MM-induced bone damage.

Lumbar spine and hip BMD mean values have been >1% higher with respect to baseline both at six and at twelve months. Although BMD mean values have been higher at six than at twelve months, lumbar spine BMD mean values have continuously increased during the treatment. These data suggest that NER, if administered at these doses and timing, might allow at least for one year sustained BMD increases in patients with MM and initial skeletal damage. Indeed, the steady reduction of tAF plasma levels indicates that NER might significantly inhibit bone absorption in these subjects. This effect on bone metabolism may clearly appear after three months from the beginning of the treatment and would subsequently reach a plateau, as shown by the prolonged 40-50% reduction of tAF plasma levels. On the other hand, calcium plasma levels did not seem to be influenced by the treatment.

NER has been highly tolerated in this study. The almost complete absence of adverse effects has prompted us to reduce the time of infusions at the end of the study (from 150 to 15 mins). This modification did not result in an increased incidence of adverse effects of any kind.

In conclusion, this study provides the first data on the efficacy and safety of NER in patients with MM-induced bone damage. These initial data encourage wider phase III trials to clearly assess its efficacy in preventing skeletal-related events and its possible anti-neoplastic properties.

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