Novel treatment (new drug/intervention; established drug/procedure in new situation)

Teriparatide treatment complicated by malignant myeloma

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Summary

Recombinant human parathyroid hormone (1–34) (rhPTH 1–34), teriparatide (Forsteo in Europe), is a new compound that has been introduced and shown to be successful in the treatment of osteoporosis. The mechanisms of action include a pulsative influence on the RANKL/OPG system resulting in osteoblast activation and increased bone formation by teriparatide. In malignant myeloma there is an imbalance between osteoclast and osteoblast activity with involvement of the RANKL/OPG system among others. We report a case with monoclonal gammopathy of uncertain significance (MGUS) who developed malignant myeloma after teriparatide treatment and we suggest that in addition to malignant myeloma and smouldering myeloma, MGUS should also be considered contraindicated for teriparatide treatment.

BACKGROUND

This case demonstrates that mechanisms implicated in the treatment of osteoporosis with teriparatide also might be involved in development of malignant myeloma and monoclonal gammopathy of uncertain significance (MGUS). It also demonstrates that malignant myeloma and MGUS should be excluded prior to teriparatide administration and it is probable that the use of teriparatide should be contraindicated in these patients.

Osteoporosis and osteoporosis-related fractures represent a serious problem in postmenopausal women. In addition to previous treatment schedules using calcium and D-vitamin, calcitonin and bisphosphonates, new strategies, including recombinant human parathyroid hormone (1–34) (rhPTH 1–34), teriparatide (Forsteo in Europe), have been introduced to treat this entity.¹ Although a potential role for the C-terminal fragment was described, the biological action of teriparatide resides in the first two amino acids of the N-terminal of the molecule.² When given exogenously by intermittent injection, teriparatide exhibits potent anabolic effects on the skeleton with construction of new bone, as earlier reported also with rhPTH 1–34.³ Clinical experience with teriparatide given to postmenopausal osteoporosis was recently reported.⁴

An increase in the incidence of osteosarcoma has been observed in rats given teriparatide at doses 3–60 times higher than those used in humans, which was dependent upon dose and treatment duration.⁵ However, the relevance of this observation remains uncertain in humans. As a consequence of this observation, it has been recommended that teriparatide should not be given to patients who are at increased risk for osteosarcoma, including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, paediatric and young adult patients with open epiphyses, or prior external beam or implant radiation treatment involving the skeleton.¹

Previously we have reported the co-incidence of malignant myeloma in a subject given teriparatide for osteoporosis.

Consequently, we recommended that prior to teriparatide treatment the possibility of malignant myeloma should be considered in patients with osteoporosis.⁶ Here we report a case with postmenopausal osteoporosis and multiple fractures treated with teriparatide. The patient had been shown to have a benign MGUS. Later in the course it was shown that malignant myeloma had developed.

CASE

A 59-year-old woman was admitted to our hospital due to multiple spontaneous thoracic and lumbar compression fractures (Th-VI, IX, XI, XII, and L-I, LII) first observed at x-ray examination in December 2005.

Investigations

MRI examination in January 2006 confirmed this finding and was consistent with severe osteoporosis. No other bone destructions and no medullar compression were found. Bone mineral density (BMD) in the lower vertebral corpora (LII–LIV) was 0.9 g/cm² with a T-score of –2.3 and BMD in the left femur neck was 0.73 g/cm² and T-score –2.1. Routine work-up included examinations to unveil malignant myeloma. Serum protein fractioning contained no monoclonal component. Urinary protein excretion was 133 mg/litre (ref < 100 mg/litre) consisting of 590 mg/litre (ref 6.9–25.6 mg/litre) of monoclonal free κ light chain (S-IgLC κ -F) paraprotein (figure 1A). The relation between κ/λ (S-K/L-s-F) was increased to 111.0 (ref 0.52–1.4). The amount of plasma cells at bone marrow examination was <5% (figure 2A) and was interpreted as normal. In absence of any lytic lesions at x-ray examination and no other pathological laboratory findings the paraproteinuria was interpreted as benign so-called MGUS. As serum protein fraction did not contain monoclonal component a smouldering myeloma seemed unlikely.

Treatment

Since January 2006 she had been given calcium and 25-OH-D-vitamin (cholecalciferol) supplementation and

27.03.2006

U-Prot = 0.13 g/l

12.09.2007

U-Prot = 1.09 g

29.05.2009

U-Prot = 1.04 g

Figure 1 Protein fractionation in urine sampled before (A), directly following cessation (B) and later after teriparatide treatment (C).

Figure 2 Bone marrow examination at light microscope before (A, above) and about a year after discontinuation of teriparatide treatment (B) confirming malignant myeloma (May-Grünwald Giemsa, scale bar 10 μ)

alendronate for osteoporosis. However, the bisphosphonate had to be discontinued due to gastrointestinal side effects. Carvedilol and later on betaxolol had been given for

high blood pressure, which was later discontinued due to low blood pressure. In addition, different types of pain killers had been used.

Table 1 Selected laboratory results in a patient with monoclonal gammopathy of uncertain significance (MGUS) prior to, during and after teriparatide treatment

Examination	2006	2007	2008	2009	2010	
	March	June	June	July	May	January
S-prot-fr	Norm	Norm	Norm	Norm	Norm	NA
S-prot conc (g/l)	69	70	70	76	61	NA
dU-prot/24 h (mg)	133	57	112	NA	NA	NA
S-IgLcK-F (mg/l)	NA	590	1390	2040	2140	702
S-IgLcL-F (mg/l)	NA	5.3	6.0	NA	NA	7.0
S-K/L-s-F	NA	111.0	231	NA	NA	100
S-PTH (ng/l)	38	NA	NA	NA	8	NA
S-Ca-ion (mmol/l)	1.21	1.19	1.27	NA	1.54	1.23
Sed rate (mm/h)	10	9	13	21	40	2
P-creat (ámol/l)	50	52	58	75	44	

Some laboratory findings before and after treatment with teriparatide. The elevated S-IgLcK-F was considered to be related to MGUS and not malignant at that time point. dU-prot/24 h, amount of urinary protein in 24 h samples; NA, not available; norm, normal; P-creat, plasma creatinine concentration; S-IgLcK-F, serum immunoglobulin light chain κ free fraction concentration; S-Ca-ion, serum ionised calcium concentration; sed rate, sedimentation rate; S-IgLcL-F, serum immunoglobulin light chain λ free fraction concentration; S-K/L, serum κ/λ relation; S-prot-fr, serum protein fractioning; S-prot conc, serum protein concentration; S-PTH, serum parathyroid hormone concentration.

After the work-up mentioned above, teriparatide was introduced in June 2006 and continued during the next 18 months during which time she had close follow-up with blood and urine examinations (table 1). As the amount of paraprotein in the urine remained almost unchanged (figure 1B), serum protein fraction normal and no myeloma-like lytic bone lesions were found at x-ray examinations, the presence of urinary paraprotein was still considered to be due to MGUS. In spite of teriparatide treatment, the BMD deteriorated with a lumbal (LII-LIV) T-score of -4.2 and left femur neck T-score -3.4 at the end of the 18 months treatment period. Ibandronate was first prescribed as antiresorptive treatment after teriparatide but was switched to zoledronate in June 2008. Shortly before zoledronate infusion (6 months after discontinuation of teriparatide treatment) a fresh left femur neck proximal fracture and an old-established right side femur neck fracture, which had not caused any symptoms and had been unknown to both patient and physician, was discovered. Both fractures were treated by surgery.

Outcome and follow-up

At this period, the amount of urinary paraprotein had increased significantly (figure 1C) and she had developed significant hypercalcaemia. Kidney function was normal. A repeat bone marrow examination was performed, which confirmed malignant myeloma (figure 2B). Pamidronate was given intravenously resulting in a rapid normalisation of the circulating calcium level and thalidomide was introduced at a daily dose of 100 mg to treat the malignant myeloma. Both these treatment schedules are continuing. Some laboratory values at follow-ups are presented in table 1.

DISCUSSION

To our best knowledge this is the second report on malignant myeloma appearing after treatment with teriparatide. Unlike in the previous report,⁶ this patient presented with MGUS prior to teriparatide treatment as judged from the appearance of less than 10% of plasma cells in bone marrow. The possibility remains that the needle aspiration did

not hit plasma cell clones; thereby, giving a normal bone marrow picture. In any case, this report and the previous one⁶ demonstrate how difficult it might be to diagnose or define risk factors in osteoporotic patients with fractures prior to teriparatide treatment. Monoclonal component was not found in serum and, consequently, in addition to examination of serum protein fraction an examination of urinary protein fraction could be recommended in patients with fractures when planned for teriparatide treatment. Moreover, in spite of these efforts, one must keep in mind that an absence of paraprotein bands does not exclude plasma cell dyscrasia. Unfortunately, we did not search for plasma cell immune-phenotypes like CD38, CD56 and CD19,⁷ which might have been of diagnostic help in our case too. It is well known that MGUS and also smouldering myeloma might progress into active malignant myeloma within some period of time.^{8,9} In this case, the MGUS was present and it is possible that the malignant myeloma was under development at the time of teriparatide treatment initiation. In our opinion, there was no reason to believe that teriparatide per se did cause malignant myeloma but certainly it should not be used when smouldering myeloma or MGUS is present. As in our previous case,⁶ here too the γ -fraction was depressed and only a small amount of proteinuria, easily overseen, was present.

Although significant differences between the mechanisms in the development of malignant myeloma and the positive effects on increased bone formation by teriparatide exists, some of the biochemical components participating during teriparatide treatment are also involved in development of malignant myeloma. In malignant myeloma it seems that a continuous imbalance between osteoclast and osteoblast activity is present. There is an increase in receptor activator of nuclear factor κ -B ligand (RANKL) expression in osteoblasts (eventually also by plasma cells) together with a reduction in the level of its decoy receptor osteoprotegerin (OPG) resulting in an increase in the RANKL/OPG ratio leading to osteoclast activation and bone resorption. In addition, some other components like macrophage inflammatory protein-1, interleukin-3 (IL-3), IL-6 and IL-7 could contribute to over-activity of osteoclasts; thereby, being

involved in the development of bone lesions in malignant myeloma. Different from the development of malignant myeloma, teriparatide treatment produces a pulsative influence on the RANKL/OPG system resulting in osteoblast activation and increased bone formation.¹⁰ This extra stimulation of the RANKL/OPG system might potentially be harmful in MCUS subjects and in developing malignant myeloma.

Hypercalcaemia is often recognised in patients with malignant myeloma. It has been demonstrated that some patients with malignant myeloma have increased levels of PTH-related peptide together with hypercalcaemia. Beaudreuil and coworkers presented a myeloma case¹¹ with high levels of PTH-related peptide in spite of correction of hypercalcaemia with bisphosphonate treatment. Our patient had normocalcaemia and a normal PTH concentration at the time of initiation of teriparatide treatment. Later in the course, when malignant myeloma was diagnosed, hypercalcaemia together with a decreased PTH level developed.

In conclusion, teriparatide is a welcome compound in the treatment of postmenopausal and other forms of osteoporosis. However, prior to such treatment, it might be wise to search for MGUS and malignant myeloma by examination of both serum and urinary protein fraction. Teriparatide might have a harmful effect on the RANKL/OPG system with unexpected effects on bone formation in patients with MGUS or malignant myeloma. The use of teriparatide treatment for osteoporosis is contraindicated in subjects with malignant bone disorders (including malignant myeloma) and, in our opinion, the list of contraindications should also include subjects with MGUS. This patient was not involved in a clinical trial.

Learning points

- ▶ Malignant myeloma and MGUS should be searched for prior to treatment with teriparatide.
- ▶ Patients with osteoporosis may have occult malignant disease.
- ▶ Following treatment with teriparatide, a close follow-up is required in order to recognise new malignant myeloma later in the course of osteoporosis.

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Patient consent Obtained.

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