Increased bone mineral density in a subset of patients with relapsed multiple myeloma who received the combination of bortezomib, dexamethasone and zoledronic acid

Bone disease is a major complication of multiple myeloma (MM) [1]. Bortezomib is the first-in-class proteasome inhibitor, with established anti-myeloma activity and beneficial effect on bone metabolism in preclinical studies [2]. In the clinical setting, bortezomib increases bone formation markers, reduces serum levels of osteoblast inhibitor dickkopf-1 [3], increases osteoblast counts in trephine biopsies [4] and inhibits osteoclast function [3, 5]. However, there are no data for bortezomib effect on bone mineral density (BMD) of myeloma patients. To evaluate this effect, we studied 27 consecutive patients (16 males/11 females; median age 69.5 years) with relapsed MM who received the combination of bortezomib plus dexamethasone (VD) and zoledronic acid (ZA): 17 had immunoglobulin G, 6 immunoglobulin A, 3 light-chain and 1 non-secretory MM. Seven patients had International Staging System-1 (ISS-1) MM at diagnosis, while 9 had ISS-2 and 11 ISS-3 MM. The median number of previous lines of therapies was 2 (range 1–5). Bortezomib was given at the standard dose of 1.3 mg/m² on days 1, 4, 8 and 11 of a 21-day cycle, while dexamethasone was given at a dose of 20 mg, p.o., the day of bortezomib administration and the following day. All patients received monthly ZA according to their renal function.

BMD of the lumbar spine (L1–L4, anteroposterior view) and femoral neck (FN) was measured by dual energy X-ray absorptiometry (DXA) using a Hologic QDR-1000 scanner at baseline (days −7 to day 1 of cycle 1) and then on day 21 of cycle 4 and 1 month after cycle 8. Evidence of myeloma bone disease at the time of relapse was documented by plain radiography. All patients had measurements of urinary N-telopeptide of collagen type-I (NTX; a sensitive bone resorption marker) and serum bone-specific alkaline phosphatase (bALP) and osteocalcin (OC) (bone formation markers), pre-VD and every month post-VD, using enzyme-linked immunosorbent assay methodology as previously described [3,5]. Differences between pre- and post-treatment values of the studied parameters were evaluated using the Wilcoxon rank sum test. The study was conducted with ethical committee approval and under the guidelines of the Declaration of Helsinki.

Figure 1. The administration of bortezomib with dexamethasone resulted in a significant increase of L1–L4 bone mineral density (BMD) after eight cycles of therapy (A). Four patients (blue lines; B) showed at least 10% of increase in L1–L4 BMD (median 16%).
At baseline, skeletal survey revealed that 8 patients (29%) had lytic lesions in 1–3 areas (group A), 18 (66%) had lytic lesions in >3 areas and/or a pathological fracture (group B), while 1 patient had diffuse osteoporosis only. DXA measurements showed that 7 patients (25%) had osteopenia and 14 (51%) had osteoporosis at least in one of the evaluated sites at the time of relapse, according to World Health Organization criteria.

All patients received eight cycles of therapy. Dose reductions of bortezomib were necessary for six patients due to side-effects (five of six patients due to peripheral neuropathy). Twenty patients achieved an objective response [partial response (PR) + complete response (CR)], while two patients had a minimal response and five patients had stable disease after eight cycles of therapy. The combination of VD plus ZA produced an increase in L1–L4 BMD after eight cycles of therapy ($T$ score mean ± standard deviation: from $-2.59 \pm 1.32$ at baseline to $-2.31 \pm 1.30$ after eight VD cycles; $P < 0.01$; Figure 1A); this increase was not observed in the FN-BMD. Four patients (14%) showed at least 10% of increase in L1–L4 BMD (median 16%; Figure 1B). All these patients had osteoporosis according to DXA, responded to therapy (3 PR/1 CR), received VD as second-line treatment and regarding osteolytic disease, three patients belonged to group A, while one had only diffuse osteoporosis. Similarly, NTX was reduced after eight cycles of the combination (from $49.3 \pm 41.4$ at baseline to $40.7 \pm 15.65$ nM bone collagen equivalent/mM creatinine; $P = 0.013$), while both bone formation markers were markedly increased (bALP: from $15.2 \pm 4.2$ to $19.2 \pm 5.9$ U/l, $P < 0.01$; OC from $9.4 \pm 6.7$ to $19.8 \pm 9.8$ ng/ml, $P < 0.01$).

In conclusion, our study shows for the first time in the literature that the combination of VD plus ZA increases BMD in a subset of relapsed MM patients with low BMD and non-extensive lytic disease who received this regimen at first relapse. This BMD improvement was observed very early, in ~6 months post-initiation of therapy, and has not been described with other anti-myeloma regimens even in responding patients. Based on these results, a prospective study evaluating BMD in patients with relapsed myeloma who receive VD as second-line therapy has just started.

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disclosure

ET has received honoraria from Janssen-Cilag, Novartis and Amgen. MAD has received honoraria from Janssen-Cilag and Novartis.

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