Optimizing bone health in lymphoma survivors: denosumab superiority to alendronate for R-CHOP-like therapy (the DENOSULY phase III randomized controlled trial)

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Abstract

Glucocorticoid-induced osteoporosis (GIOP) is a critical long-term complication in lymphoma survivors, with a substantial cumulative incidence of fractures following R-CHOP-like therapy. Existing guidelines on the treatment of GIOP, typically based on chronic low-dose steroid use, are insufficient for managing this acute, high-risk lymphoma therapy-related (LTR) toxicity. This prospective, multicenter, phase III randomized controlled trial of 100 patiemts (median age 74 years) compared the efficacy and safety of denosumab *versus* alendronate in newly diagnosed lymphoma patients receiving R-CHOP-like therapy. Patients were randomized into two groups: one received two subcutaneous injections of denosumab at a 6.month interval, and the other received oral alendronate once a week for 12 months. This study was named DENOSULY and the cases were collected by the Hokuriku Hematology Oncology Study Group. The primary endpoint was the percentage change in lumbar spine bone mineral density at 12 months. Denosumab demonstrated superiority over alendronate in lumbar spine (L1-L4) bone mineral density change (denosumab: +2.8%±4.4% *vs*. alendronate: −1.3%±5.6%; *P*=0.0010). Crucially, denosumab also showed superiority at the femoral neck (denosumab: +2.8%±5.8% *vs*. alendronate: −3.6%±10.3%; *P*=0.0020), a site where superiority is infrequently demonstrated in non-LTR-GIOP comparisons. Denosumab achieved stronger suppression of the bone resorption marker TRACP-5b (*P*=0.0003). Since denosumab showed significant superiority over alendronate at both the lumbar spine and femoral neck, denosumab may be the preferred agent in LTR-GIOP. Recognizing R-CHOP recipients as a very high-risk population, our findings underscore the need for immediate, enhanced prophylaxis with denosumab to prevent LTR-GIOP and improve long-term survivorship and quality of life. This trial was registered at *www.umin.ac.jp* as UMIN000038881.

Introduction

The introduction of rituximab has transformed the treatment of B-cell lymphomas. For instance, the R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) regimen has significantly improved survival outcomes in patients with diffuse large B-cell lymphoma (DLBCL).[1,2] However, this success has been accompanied by long-term complications, specifically the decrease in bone mineral density (BMD) associated with chemotherapy.

In the treatment of lymphoma, corticosteroids are indispensable, serving a dual role: they exert a powerful cytotoxic effect that kills lymphoma cells and, concurrently, mitigates the side-effects of chemotherapy such as nausea and vomiting. On the other hand, the detrimental effect of steroids on bone – specifically, glucocorticoid-induced osteoporosis (GIOP) – is the most common cause of iatrogenic osteoporosis and is estimated to occur in

approximately 30-50% of chronic steroid users.[3] This steroid-induced imbalance in bone remodeling results in a characteristic rapid loss of bone mass within a short period.[4] Despite the well-known effects of steroids on bone, the impact of steroid-containing lymphoma treatment on BMD reduction has not been sufficiently addressed until recently, with several important clinical studies examining this issue having been published in recent years.

Prospective studies have demonstrated a significant reduction in BMD within the first year of chemotherapy in lymphoma patients.[5] This reduction was particularly pronounced in patients receiving a higher number of cycles and those of older age.[6]

Importantly, this BMD reduction was associated with bone-related events. Specifically, long-term registry studies involving survivors of DLBCL and follicular lymphoma treated with R-CHOP-like regimens demonstrated a significantly elevated 10-year cumulative risk of osteoporotic events compared to that in the general population (16.3% *vs*. 13.5%).[7] Furthermore, a retrospective analysis targeting elderly DLBCL patients treated with R-CHOP revealed an alarming cumulative fracture incidence of 11.4% at just 18 months after treatment.[8] Moreover, a significant proportion of patients (23%) had pre-existing fractures prior to treatment, which were often unrecognized and dramatically increased the risk of new fractures during therapy.[9] As recently demonstrated by Douglas *et al*. using opportunistic bone density assessment on routine staging by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), the early identification of skeletal fragility in lymphoma patients is becoming an established clinical possibility.[10] However, while identifying at-risk patients is increasingly achievable, definitive evidence for the "optimal interventional agent" to manage these high-risk individuals remains insufficient.

To mitigate BMD loss, several intervention trials have evaluated bisphosphonates. While agents such as alendronate,[11] pamidronate,[12] and zoledronic acid[13] have shown efficacy in stabilizing BMD, definitive evidence for the optimal interventional agent in this high-risk population remains insufficient.

Denosumab is an osteoporosis treatment with a mechanism of action distinct from that of bisphosphonates. It is a monoclonal antibody that suppresses osteoclast function by neutralizing receptor activator of NF-kB ligand (RANKL), which is essential for the formation, activation, and survival of bone-resorbing osteoclasts. We previously conducted a non-randomized prospective study evaluating the efficacy of denosumab in lymphoma patients.[14] In this study, we stratified 43 newly diagnosed lymphoma patients receiving steroid-containing chemotherapy by T-score: patients with a baseline T-score of ≤-1 received denosumab, and patients with a T-score of >-1 were assigned to a non-intervention group. The results indicated that while BMD reduction was observed in the lumbar spine and femoral neck of patients in the non-intervention group, BMD remained stable in patients in the denosumab group. This study suggested that denosumab is a promising option for lymphoma therapy-related GIOP (LTR-GIOP). However, caution was required when interpreting the results obtained given the non-randomized design of the study. Furthermore, the intervention group included more elderly patients who were at a higher risk of bone loss, thereby limiting strict scientific comparison. This previous work served as a crucial pilot study, the results of which provided the clinical rationale for the design of our current phase III trial.

The four aforementioned intervention trials offered different levels of evidence. The pamidronate study provided the strongest clinical rationale, as it demonstrated a reduction not only in the surrogate marker of BMD improvement but also in the clinically relevant endpoint of fracture.[12] The SIESTA trial also confirmed that oral bisphosphonates stabilize BMD, although with the caveat that this surrogate endpoint alone may not correlate with fracture reduction in small cohorts[11] The zoledronic acid study, a randomized controlled trial with a phase III design, provided high-quality evidence indicating that prophylactic intervention is effective in stabilizing BMD.[13] In contrast, our previous work with denosumab was a pilot/proof-of-concept study, resulting in a lower level of evidence.[14] To obtain higher quality evidence, we therefore conducted a multicenter phase III trial comparing denosumab and alendronate, which was evaluated in the aforementioned SIESTA trial.[11]

Methods

Detailed methods are available in the *Online Supplementary Appendix*.

Study design and objectives

This prospective, multicenter, randomized, open-label phase III trial compared the efficacy and safety of denosumab *versus* alendronate in newly diagnosed lymphoma patients undergoing corticosteroid-containing chemotherapy. The primary endpoint was the 12-month percentage change in lumbar spine BMD (comparison to baseline). Secondary endpoints included BMD changes at the femoral neck and total hip at 6 and 12 months, and changes in markers of bone turnover at 6 months. The protocol was approved by the Institutional Review Board of Toyama University Hospital (protocol N R2019137) and registered at UMIN-CTR (ID: UMIN000038881). All participants provided written informed consent.

Patients and treatment

We enrolled newly diagnosed lymphoma patients aged ≥65 years scheduled for steroid-containing chemotherapy. Key exclusion criteria included hypersensitivity to denosumab or bisphosphonates, baseline hypocalcemia, or current

osteoporosis treatment. Patients were stratified by age (≥80 years) and sex, then randomized (permuted block method) to receive either denosumab 60 mg subcutaneously at baseline and at 6 months or alendronate 35 mg orally once weekly for 12 months. All patients received daily oral calcitriol (0.25 μg) for 12 months. BMD was assessed by dual-energy X-ray absorptiometry. Markers of bone turnover included tartrate-resistant acid phosphatase 5b (TRACP-5b) and total type I procollagen N-terminal propeptide (total P1NP).

Adverse events

Adverse events were categorized following standard criteria (see *Online Supplementary Methods*). Predetermined adverse events of interest (grade ≥3) included hypocalcemia and osteonecrosis of the jaw (ONJ). Standard chemotherapy-related toxicities (e.g., myelosuppression) were not reported unless serious.

Rationale for target sample size

The sample size was determined by referencing a comparative study of denosumab and alendronate for patients with nephritis.[15]

Statistical methods

Statistical analyses were performed used GraphPad Prism v9.0. Values are presented as the mean ± standard deviation. Significance was determined by a Student's *t* test (normal distribution) or Mann-Whitney U test. Categorical variables were evaluated by Fisher's exact test and correlations by Spearman's coefficient. All tests were two-sided and $P<0.05$ was considered statistically significant.

Results

Enrollment, allocation, and follow-up of patients

The disposition of the 100 patients initially recruited in this study is shown in Figure 1.

Characteristics of the patients

There were 48 patients in the alendronate group and 52 patients in the denosumab group, of whom 54.2% and 55.8%, respectively, were male. Their median age was 75 and 73 years, and the proportion of DLBCL among lymphoma subtypes was 93.8% and 84.6%, respectively. No statistically significant differences were found between the two groups for any of these characteristics. BMD was measured for the lumbar spine (L2-L4 and L1-L4), total hip, and femoral neck, and markers of bone turnover, TRACP-5b and total P1NP, were assayed. No significant differences were observed between the alendronate and denosumab groups for any of these parameters. Similarly, the cumulative dose of prednisolone did not differ significantly between the two groups (Table 1). A detailed breakdown of lymphoma histology and treatment regimens is provided in *Online Supplementary Table S1*.

Bone turnover markers

Figure 2 illustrates the percentage change in markers of bone turnover at 6 months after initiation of the study. For

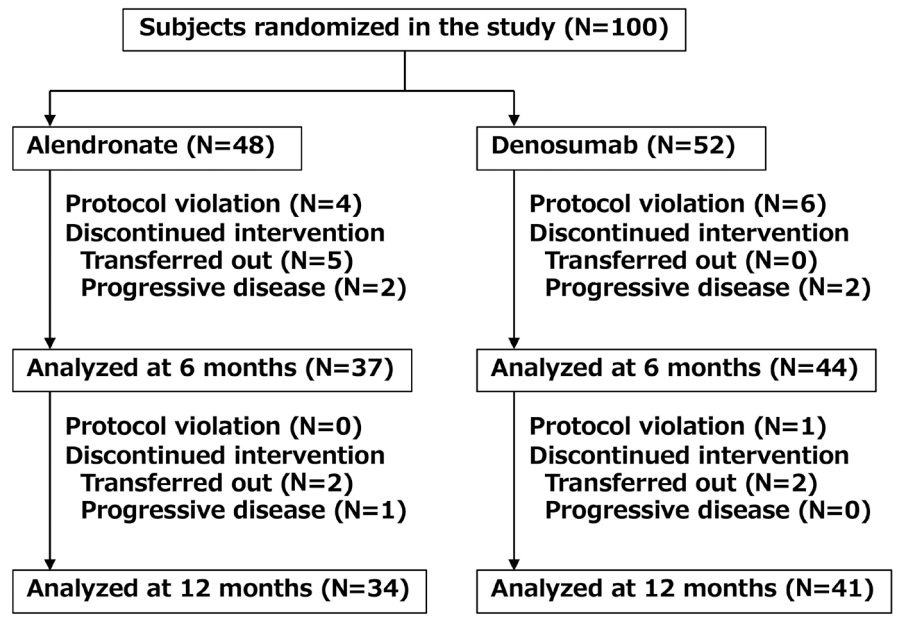

Figure 1. Patients' disposition and study flow diagram. CONSORT (Consolidated Standards of Reporting Trials) flow diagram illustrating the enrollment, randomization, and follow-up of patients in the alendronate and denosumab groups.

Table 1. Characteristics of the patients.

Characteristics	Alendronate N=48	Denosumab N=52	*P*
Age, years, median (range)	75 (64-87)	73 (62-86)	0.978
Male sex, N (%)	26 (54.2)	29 (55.8)	0.872
Type of lymphoma, N (%)			0.144
DLBCL	45 (93.8)	44 (84.6)	
Others	3 (6.2)	8 (15.4)	
Follicular lymphoma	1	1	
PTCL	1	3	
AITL	1	1	
Burkitt lymphoma	0	1	
IVLBCL	0	2	
BMD, g/cm^2, mean (±SD)			
L2-4	1.14 (±0.30)	1.12 (±0.24)	0.654
L1-4	1.13 (±0.29)	1.11 (±0.21)	0.720
Total hip	0.84 (±0.14)	0.86 (±0.18)	0.480
Femoral neck	0.77 (±0.15)	0.78 (±0.20)	0.768
BTM, mean (±SD)			
TRACP-5b, mU/dL	468 (±216)	412 (±165)	0.142
total P1NP, ng/mL	53.1 (±30.3)	53.2 (±24.7)	0.977
Cumulative dose of prednisolone, mg, mean (±SD)	2,707 (±706)	2,565 (±721)	0.386

AITL: angioimmunoblastic T-cell lymphoma; BMD: bone mineral density; BTM: bone turnover marker; DLBCL: diffuse large B-cell lymphoma; IVLBCL: intravascular large B-cell lymphoma; PTCL: peripheral T-cell lymphoma; P1NP: procollagen type 1 N-terminal propeptide; SD: standard deviation; TRACP-5b: tartrate-resistant acid phosphatase 5b.

TRACP-5b (Figure 2A), the alendronate group showed 0±44% change, while the denosumab group showed -36±42%, indicating that denosumab suppressed TRACP-5b significantly more than alendronate did (*P*=0.0003). In contrast, no significant difference was observed between the two groups for total P1NP (Figure 2B).

Bone mineral density

Online Supplementary Figure S1 shows the percentage change in BMD at 6 months after initiation of the study. There were no significant differences between the alendronate and denosumab groups for L2-L4, L1-L4, and total hip BMD (*Online Supplementary Figure S1A-C*). However, at the femoral neck (*Online Supplementary Figure S1D*), the alendronate group showed -1.9±6.7% change, and the denosumab group showed 4.5±16.3% demonstrating that denosumab significantly increased BMD compared to alendronate (*P*=0.0338). Significantly, the superiority of denosumab over alendronate became even more pronounced at 12 months after starting the study (Figure 3). Specifically, denosumab was superior to alendronate in L2-L4, L1-L4, and femoral neck, excluding the total hip. In detail, the changes in BMD in the alendronate and denosumab groups were: for L2-L4 -1.3±5.6% and -1.3±5.6% and 2.8±4.4%, respectively (*P*=0.0010); for L1-L4, -1.0±4.8% and 2.7±4.5%, respectively (*P*=0.0054); and for the femoral neck, -3.6±10.3% and 2.8±5.8%, respectively (*P*=0.0020). Subgroup analysis of patients with DLBCL (N=89) yielded results consistent with the findings in the overall population (*Online Supplementary Figure S2*).

Correlation analysis

These results suggest a model in which denosumab prevents BMD reduction or induces BMD increase by substantially lowering TRACP-5b among markers of bone turnover, thereby sufficiently suppressing osteoclast-mediated bone resorption. We, therefore, analyzed whether the reduction in TRACP-5b at 6 months correlated with the increase in BMD at 12 months in the denosumab group using simple linear regression (Table 2). Contrary to expectations, the percentage change in BMD at 12 months did not correlate with the percentage change in TRACP-5b at 6 months in any of the sites measured: L2-L4, L1-L4, total hip, and femoral neck. Furthermore, it did not correlate with the percentage change in total P1NP at 6 months, the total cumulative dose of corticosteroids, or the baseline BMD prior to treatment initiation. Conversely, patient age showed a weak negative correlation with the percentage change in L2-L4 and L1-L4 BMD. The specific correlation graphs are shown in *Online Supplementary Figure S3*. The correlation coefficients were -0.384 (*P*=0.0131) for L2-L4 and -0.342 (*P*=0.0409) for L1-L4.

Adverse events

Regarding serious adverse events (Table 3), it is important to note that, as predefined in our protocol and *Online Supplementary Methods*, common chemotherapy-related toxicities such as myelosuppression were only reported as serious adverse events if they met strict criteria for being 'serious' (e.g., resulting in hospitalization or life-threatening events). Based on these criteria, the alendronate group had one patient with grade <2 events and nine patients with grade ≥3 events. The denosumab group had 0 patients with grade <2 events and ten patients with grade ≥3 events. In all cases, no direct causal relationship was suspected between the adverse events and alendronate or denosumab. Notably, the three neoplasms observed in the denosumab group were gastric cancer (1 patient), colorectal cancer (1 patient), and esophageal cancer (1 patient). All three were discovered during the pre-treatment systemic screening performed for staging purposes, prior to denosumab administration. Endoscopic or surgical treatments were subsequently performed following chemotherapy for lymphoma. *Online Supplementary Table S2* presents the characteristic adverse events associated with alendronate and denosumab. Two particular items of note are hypocalcemia and ONJ. Regarding these adverse events of interest, no cases of grade ≥3 events were reported.

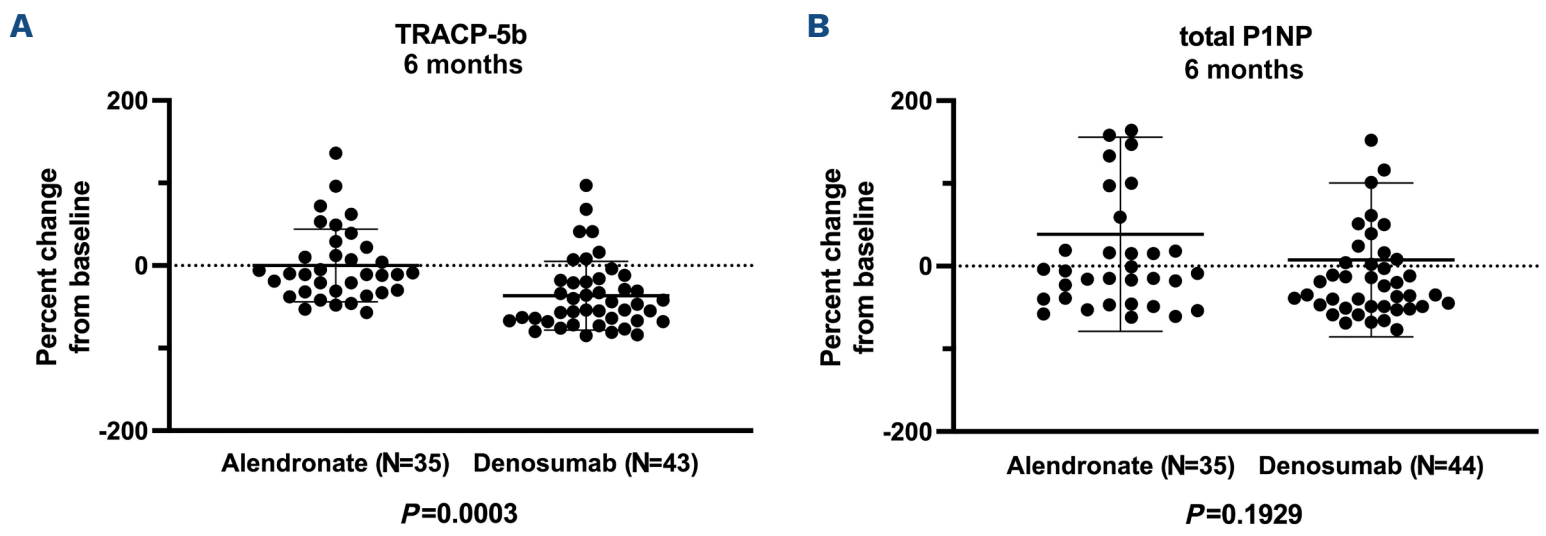

Figure 2. Comparison of percentage changes in bone turnover markers at 6 months. (A, B) Percentage change from baseline in TRACP-5b (A) and total P1NP (B) between the alendronate and denosumab groups.

Discussion

This study is the first randomized controlled trial to demonstrate the superiority of denosumab over alendronate in preventing GIOP in newly diagnosed lymphoma patients receiving steroid-containing chemotherapy. Denosumab significantly surpassed alendronate in the primary endpoint, the percentage change in lumbar spine BMD at 12 months. Similar superiority was also demonstrated at the femoral neck.

The main therapeutic options for GIOP include bisphosphonates and denosumab. Bisphosphonates (e.g., alen-

Table 2. Correlation analysis of percent change of bone marrow density at 12 months.

	BMD at 12 months, %			
	L2-L4 (%)	L1-L4 (%)	Total hip (%)	Femoral neck (%)
Age (year)	–0.384*	–0.342*	–0.119	0.110
Total prednisolone (mg)	0.233	0.243	0.277	0.049
BMD at baseline (g/cm^2)				
L2-L4	–0.047	0.041	–0.306	–0.072
L1-L4	0.025	–0.014	–0.330	–0.324
Total hip	–0.122	–0.163	0.177	–0.074
Femoral neck	–0.154	–0.077	0.285	0.006
BTM at 12 months (%)				
TRACP-5b	–0.190	–0.062	–0.059	–0.072
Total P1NP	–0.076	–0.086	–0.210	–0.094

*P<0.05. BMD: bone mineral density; BTM: bone turnover marker; PSL: prednisolone; P1NP: procollagen type 1 N- terminal propeptide; TRACP-5b: tartrate-resistant acid phosphatase 5b.

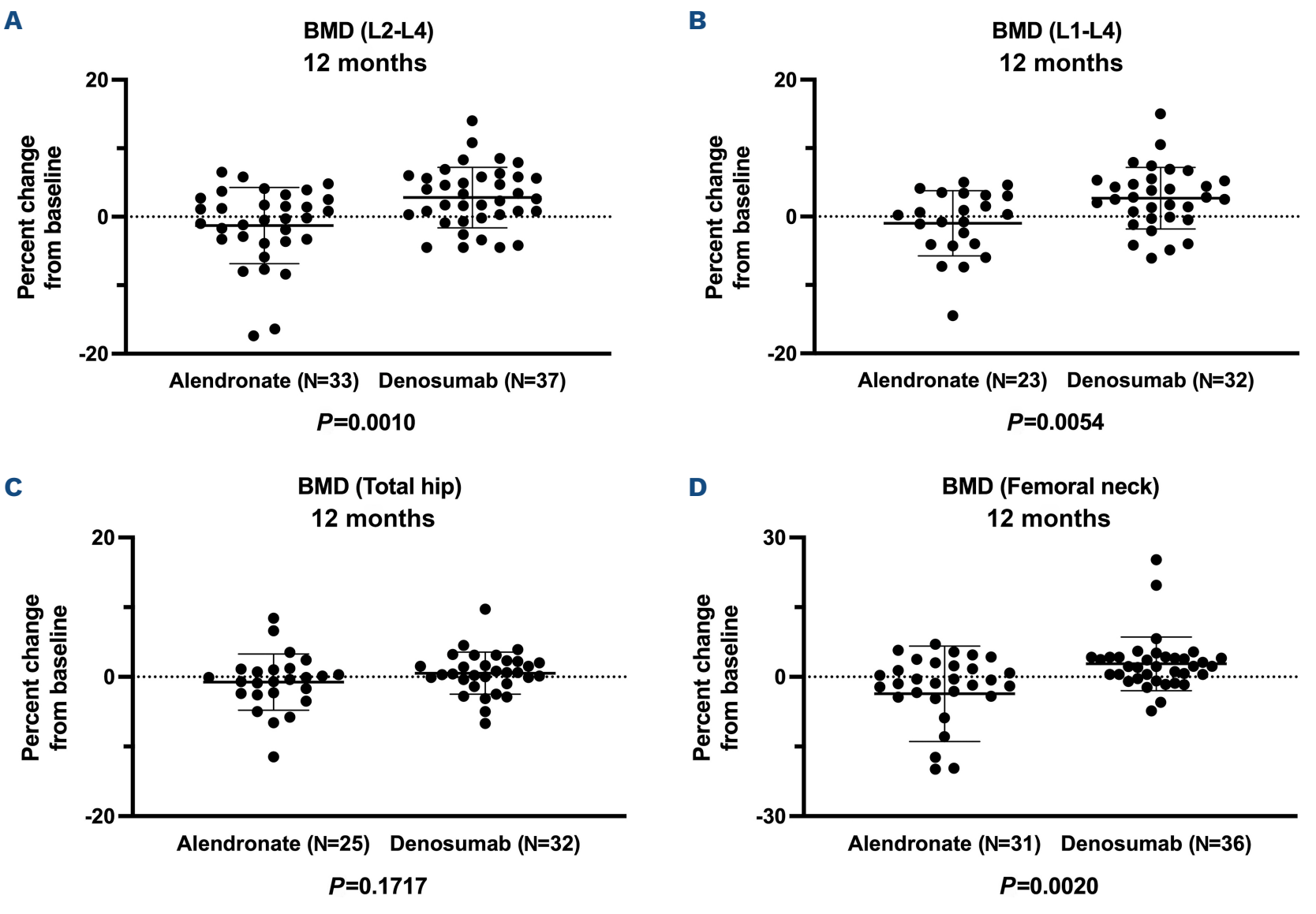

Figure 3. Comparison of percentage changes in bone mineral density at 12 months. Percentage change in bone mineral density from baseline between the alendronate and denosumab groups at (A) L2–L4, (B) L1–L4, (C) total hip, and (D) femoral neck. BMD: bone marrow density.

dronate, risedronate, etidronate, zoledronate) suppress bone resorption by depositing onto the bone surface and inhibiting specific enzymes, such as farnesyl pyrophosphate synthase, within osteoclasts.[16] Denosumab, on the other hand, is a fully humanized monoclonal antibody that specifically binds to and inhibits the function of RANKL, a key regulator of bone metabolism. This interaction leads to the suppression of osteoclast formation, function, and survival, resulting in a powerful inhibition of bone resorption and a subsequent increase in BMD.[17]

Concerning non-LTR-GIOP, multiple meta-analyses report that denosumab is superior to bisphosphonates in improving lumbar spine BMD.[18,19] However, results regarding femoral BMD remain inconsistent; while one meta-analysis showed denosumab superiority,[18] another found no significant difference between the two agents.[19] This divergence may be explained by the lower proportion of metabolically active trabecular bone in the femoral neck compared to the lumbar spine.[20,21]

In contrast, our current data on LTR-GIOP demonstrated that denosumab was significantly superior to alendronate at both the lumbar spine and, notably, the femoral neck at 6 and 12 months. This striking difference suggests that BMD degradation in LTR-GIOP may be pathologically more severe than in non-LTR-GIOP, acutely affecting even cortical bone integrity. Indeed, the reported 1-year femoral neck BMD reduction in rheumatoid patients (non-LTR-GIOP) was -1.40%,[22] whereas it reached -2.2% in LTR-GIOP patients.[5]

We hypothesize that the intensive nature of LTR-GIOP (high-dose pulse therapy: 100 mg prednisolone/day for 5 days, repeated every 21 days) may exert a more profound skeletal toxicity than previously assumed. This cyclical high-dose regimen may cause unexpectedly rapid and intense suppression of bone formation. For instance, high-dose methylprednisolone can reduce bone formation markers by over 50–80% within just 2 days.[23] Our findings suggest that in the context of such profound bone-turnover suppression characteristic of LTR-GIOP, the potent anti-resorptive effect of denosumab provides a crucial advantage over alendronate in preserving both trabecular and cortical bone.

Denosumab is widely approved as an anti-osteoporosis agent, yet strong concerns persist among clinicians involved in treating multiple myeloma and solid tumors with bone metastases regarding adverse events such as hypocalcemia and ONJ. This apprehension arises because denosumab is used in these oncology settings at the “oncology dose” of 120 mg subcutaneously every 4 weeks, a regimen frequently associated with such toxicities. Indeed, according to a data-integrated analysis of three major randomized, phase III trials involving patients with breast cancer, prostate cancer, other solid tumors, or multiple myeloma, the incidence of severe (grade 3 or 4) hypocalcemia in the denosumab arm was reported to be 3.1%, and the overall incidence of ONJ was reported to be 1.8%.[24]

However, the regimen adopted in the present study for LTR-GIOP prophylaxis is the standard dose for osteoporosis, which is 60 mg subcutaneously every 6 months. A key report demonstrating the safety of this “osteoporosis dose” involves a multicenter, double-blind study of men receiving androgen deprivation therapy for prostate can-

Table 3. Serious adverse events.

Event	Alendronate, N=48		Denosumab, N=52	
	Grade <2 N (%)	Grade ≥3 N (%)	Grade <2 N (%)	Grade ≥3 N (%)
Blood bilirubin increased	0 (0)	0 (0)	0 (0)	1 (1.9)
Neutrophil count decreased	0 (0)	1 (2.1)	0 (0)	1 (1.9)
Lung infection	0 (0)	2 (4.1)	0 (0)	1 (1.9)
Viremia	0 (0)	0 (0)	0 (0)	1 (1.9)
Biliary tract infection	0 (0)	0 (0)	0 (0)	1 (1.9)
Heart failure	0 (0)	1 (2.1)	0 (0)	0 (0)
Atrial fibrillation	1 (2.1)	0 (0)	0 (0)	0 (0)
Enterocolitis	0 (0)	1 (2.1)	0 (0)	0 (0)
Cholecystitis	0 (0)	1 (2.1)	0 (0)	0 (0)
Brain contusion	0 (0)	0 (0)	0 (0)	1 (1.9)
Adjustment disorder	0 (0)	1 (2.1)	0 (0)	0 (0)
Disease progression	0 (0)	2 (4.2)	0 (0)	1 (1.9)
Neoplasms	0 (0)	0 (0)	0 (0)	3 (5.8)
Total	1 (2.1)	9 (18.8)	0 (0)	10 (19.2)

cer.[25] The results showed that, in association with denosumab treatment, the incidence of grade 2 hypocalcemia was less than 1%, and no cases of ONJ were reported.

In our phase III trial targeting LTR-GIOP, no serious adverse events of grade ≥3, including hypocalcemia and ONJ, were observed in the denosumab group (*Online Supplementary Table S2*). This result clearly demonstrates that the "osteoporosis dose" of denosumab used for LTR-GIOP prophylaxis can safely deliver the high BMD increase observed in our study. Therefore, excessive concern regarding severe adverse events should not be a barrier to the adoption of denosumab in the management of bone health of lymphoma survivors.

The findings of this study may have important implications for existing guidelines and clinical practice recommendations regarding the treatment of GIOP. Many clinical guidelines, including those from the American College of Rheumatology[26] and the Japanese Society for Bone and Mineral Research,[27] recommend bisphosphonates and denosumab as equivalent options for the prevention and treatment of GIOP. These recommendations are primarily based on evidence derived from patient populations administered relatively low doses of steroids over a long period, such as patients with rheumatoid arthritis or asthma.

However, in the treatment protocol for lymphoma, high doses of steroids, such as 100 mg of prednisolone per day, are administered to patients short-term and cyclically. This unique administration regimen may induce a bone metabolism pathology that differs from that of the conventional GIOP model. It is, therefore, necessary to reconsider whether the aforementioned guidelines and clinical practice recommendations should be applied directly to LTR-GIOP.

Indeed, previous meta-analyses reported no significant difference between the two agents regarding femoral neck BMD.[19] However, our study demonstrated the superiority of denosumab over alendronate in LTR-GIOP, not only at the lumbar spine but also at the femoral neck. The results of this study suggest that in the specific clinical scenario of lymphoma treatment, the two therapeutic agents should not be recommended as equivalent, and that denosumab may be a better choice. Thus, existing guidelines might need to be amended or revised to include additional considerations for LTR-GIOP.

We propose that future guidelines should explicitly recommend enhanced intervention, classifying R-CHOP recipients as a "very high risk" population, necessitating the consideration of powerful antiresorptive agents such as denosumab, deviating from the typical stepwise approach often recommended for chronic low-dose glucocorticoid users.

This study yielded important clinical insights into the comparison of denosumab and bisphosphonates in LTR-GIOP. However, several limitations must be considered regarding the generalizability of our findings. First, the number of patients examined in this study may result in insufficient statistical power. Furthermore, direct clinical outcomes, most importantly fractures, were not examined, which remains a primary limitation of this study. Second, a slightly higher tendency to dropout was observed in the bisphosphonate group than in the denosumab group. This difference in dropout rates cannot be ruled out as a potential factor influencing the final efficacy assessment between the two groups. Third, the bisphosphonate chosen for comparison in this study was only alendronate, while other more potent bisphosphonates, such as zoledronate, were not selected for comparison.

To overcome these limitations and validate the hypotheses derived from this study, a larger, long-term, multicenter randomized controlled trial targeting LTR-GIOP patients is necessary. Such a large-scale study should set fracture risk reduction as the primary endpoint and would require detailed evaluation of the long-term safety profile and cost-effectiveness of both agents. Furthermore, zoledronate would be an appropriate comparator for denosumab, as it is administered intravenously. This route of administration would allow for a more precise evaluation of efficacy by eliminating the concerns associated with poor adherence to oral medications – a common challenge in long-term GIOP prophylaxis.

In summary, this study represents the first clinical trial comparing denosumab and alendronate specifically in LTR-GIOP. Importantly, we found that denosumab had a superior BMD-increasing effect compared to bisphosphonates, even at the femoral neck, a site typically considered less metabolically active. This may be related to the high-dose, cyclical steroid administration characteristic of lymphoma treatment. Given these findings, denosumab may be particularly beneficial for patients with a low baseline BMD at the femoral neck, who are at a higher risk of hip fractures during or after intensive chemotherapy.

In conclusion, our data complement the recommendations of general GIOP practice guidelines. For this specific population – patients with LTR-GIOP –denosumab should perhaps be more actively recommended over alendronate, with the suggestion that individualization of intervention is crucial for the effective management of fracture risk in this group.

Disclosures

No conflicts of interest to disclose.

Contributions

TS conceived and designed the study. RH, TF, YN, TMin, KO, YK, and AK collected the data. SK and EN analyzed and interpreted the data. TS and NHD drafted the manuscript. YM, TMiy, and TY verified the data. All authors contributed to revisions of the manuscript, and read and approved the final version of the manuscript.

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in data collection and analysis.

Data-sharing statement

The datasets generated and/or analyzed during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

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