Effect of Denosumab Administration on Lumbar Vertebral Strength of Patients with Vertebral Bony Metastases: Preliminary Study

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Abstract. *The purpose of this study was to examine the usefulness of administration of denosumab (antibody against tumor necrosis factor superfamily member 11) as a preventative therapy for skeletal-related events (SREs), such as fracture or paralysis, by computed-tomography (CT)-based on the finite element method (FEM). Patients who had undergone treatment for vertebral metastases with denosumab administration from December 2013 to August 2015 at our Institution were reviewed. We investigated patient data at the time before denosumab administration and at 1, 3 and 6 months using CT. A total of six patients were eligible; four males and two females, with ages ranging from 35 to 73 years, with a mean age of 56 years. Repeated measures analysis of variance showed a significant increase (p=0.0055, F=10.67). To our knowledge, this is the first article to substantiate the effects of the SRE-preventative drug denosumab.*

There are now multimodal therapy options for various cancer types, hence the prognosis of patients is accordingly assumed to be longer than in the past. However, the issue of how to treat bone metastases in patients with advanced cancer has not yet been resolved. In particular, there is the problem of poor activities of daily living due to skeletal-related events (SRE) such as fracture or paralysis resulting from vertebral collapse. Preventative therapy for SREs is widespread nowadays. In a randomized controlled trial of high-risk males with castration-resistant prostate cancer, treatment with denosumab was associated with improved bone metastasis-free survival (1). However, no surrogate has been validated yet for forecasting the likelihood of SREs.

Computed tomography (CT)-based finite element method (FEM) has recently been developed as a useful and non-invasive method for estimating bone strength in osteoporotic bone (2-5). A bone's strength, by which osteoporotic bone could be evaluated accurately based on CT-based FEM, might be one reliable surrogate for establishing appropriate timing for preventive therapy. However, there have been no studies applying CT-based FEM to bone metastasis as far as we are aware of.

We have established a Cancer Board at our hospital, and organized a new cooperative system to follow-up patients with advanced cancer for long periods for the purpose of maintaining their activities of daily living (ADL). In this system, we are able to evaluate time-dependent changes of bone strength by CT-based FEM.

The purpose of this study was to examine the usefulness of denosumab administration for preventative therapy of SRE, such as fracture or paralysis, using CT-based FEM.

Patients and Methods

Patient data. This prospective study protocol was approved by the Institutional Review Board (2013-H217). Patients who had undergone treatment for vertebral metastases with denosumab administration from December 2013 to August 2015 at our Institution were reviewed. All cases were given histological diagnoses by biopsy before we treated skeletal metastases.

All patients were followed-up for a minimum of 6 months, and we investigated patient data at the time before denosumab administration and 1, 3 and 6 months using CT. Afterwards, we evaluated time-dependent changes in the bone strength of vertebral bony metastases and one vertebral bone with no metastasis.

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Key Words: CT-based finite element analysis, bone metastasis, bone strength, CT-based finite element method, denosumab administration.

Table I. *Clinical data for patients who had undergone treatment with denosumab administration for vertebral metastases.*

Case	1	2	3	4	5	6
Gender	Male	Female	Female	Male	Male	Male
Age (years)	67	65	73	35	52	44
Cancer site	Renal pelvis	Breast	Breast	Lung	Renal	Renal
PS	3	2	2	1	1	3
Katagiri score	6	1	1	6	5	7
Visceral or cerebral metastases	+	–	–	+	+	+
Radiotherapy	+	+	–	+	–	+
Chemotherapy	+	+	+	–	+	–
NRS before administration	8	2	7	1	10	10
CT images before administration	Osteolytic	Mixed	Osteolytic	Osteolytic	Osteolytic	Osteolytic

CT: Computed tomography; PS, performance status; NRS, Numerical Rating Scale.

Patient data including gender, age, performance status (PS) (6), primary site, laboratory data, Katagiri's score (7), presence of visceral or cerebral metastases, adjuvant treatment, Numerical Rating Scale (NRS) and CT data were surveyed. We also investigated time-dependent changes of bone resorption markers such as tartrate-resistant acid phosphatase 5b (TRAP5b) and urinary cross-linked N-telopeptide of type 1 collagen (NTx) before denosumab administration and at 1, 3 and 6 months by using withdrawing blood.

CT data of all patients were obtained with a slice thickness of 3 mm and a pixel width of 0.41 mm (X-vision SOMATOM 64 Cardiac; Siemens, Munich, Germany; 120 kV, 135 mAs, 512×512 matrix), as well as a calibration phantom (B-MAS200; Kyoto Kagaku, Kyoto, Japan) containing five hydroxyapatite rods (0, 50, 100, 150, 200 mg/cm^3) before treatment.

Patients were included if CT images were sufficiently clear, whatever their age, gender, or race. Patients having images with halation because of an artificial denture or some implant, those who had undergone past vertebral surgery, and those who demonstrated pathological vertebral fractures, were excluded. All examinations were reviewed by KK. All patients gave their informed consent for each examination and treatment.

Treatment. All patients received subcutaneous denosumab at 120 mg every 4 weeks. Daily supplementation with calcium (≥500 mg) was also given to prevent hypocalcemia.

FE modeling. In this study, MECHANICAL FINDER software (Research Center of Computational Mechanics Inc., Tokyo, Japan) was used to make FE models. In our 3D-FE models, trabecular bone was simulated using 5-mm tetrahedral elements, and the outer surface of the cortical shell was modeled using 5-mm triangular plates. Since the purpose of this study was to analyze more models of actual fractures in patients than in former studies, models with 5-mm tetrahedral elements were adopted. We used triangular shell elements on the outer surface of the cortex to represent the thin cortical shell, and also to reduce the overestimation of thickness and underestimation of the material properties of surface elements due to the resolution of clinically available CT scanners (8). The thickness of the cortical shell was set at 0.4 mm to represent the thin cortical shell because the pixel width of the CT scan images was 0.41 mm.

Non-linear material properties. Material properties of trabecular bone were essentially considered as bilinear, elastoplastic and heterogeneous. Young's modulus and the yield stress of each tetrahedral element were calculated using the equations proposed by Keller (9). A Poisson ratio of 0.4 was assumed (10). Former reports show that Young's modulus of the cortex ranged from 11 to 24 GPa or from 9 to 21 GPa (11, 12). We took Young's modulus of each triangular shell element to be equivalent to that of the adjacent tetrahedral element located beneath the shell element; the minimum Young's modulus of the shell element was set as 10 GPa. Considering non-linear analysis, the mechanical properties of the elements were assumed to be bilinear elastoplastic, and the post-yield modulus was set as 5% of the pre-yield Young's modulus.

Failure. Failure of the yield element in compression was defined when the minimum principal strain of an element was less than −10,000 microstrains, because earlier reports showed that the ultimate strain for trabecular bone loaded in compression ranged from −3000 to −27,900 microstrains, averaging −11,000 microstrains, against −9,700 to −15,000 with an average of −11,800 microstrains for cortical bone (13). The method of analyzing bone strength is shown in Figure 1.

Statistical analysis. Statistical significance of differences was evaluated with repeated measures analysis of variance (repeated-ANOVA). Analysis was performed using the PROC MIXED procedure in SAS9.4 (SAS Institute Inc., Cary, NC, USA). A *p*-value of less than 0.05 was considered statistically significant.

Results

A total of six patients were eligible. They were four males and two females with ages ranging from 35 to 73 years, with a mean age of 56 years. Patient data including gender, age, performance status, primary site, laboratory data, Katagiri's score, visceral or cerebral metastases, treatment for primary lesion and NRS are shown in Table I.

Vertebral bony metastases in five out of these six patients demonstrated increased bone strength at 6 months. The average bone strength before denosumab administration was

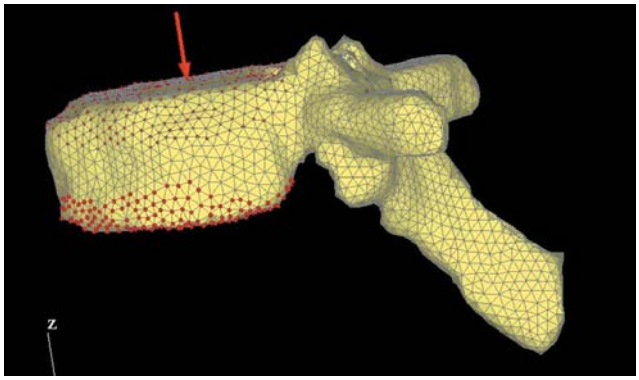

Figure 1. *A finite element model of vertebral bone in case 1, illustrating the compressed condition and loading direction. All nodes of the lower endplate of the vertebral model were completely restrained. A uniaxial compressive load with a uniform distribution and a uniform load increment was applied.*

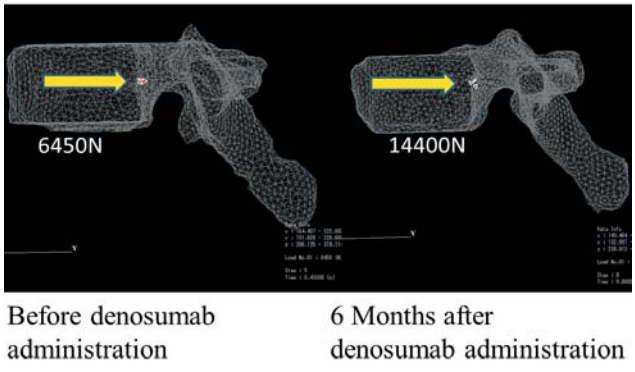

Figure 3. *The yellow arrow shows the site of bone failure in case 1 before denosumab administration and after 6 months. This case demonstrated substantial increase in bone strength as a result of denosumab administration.*

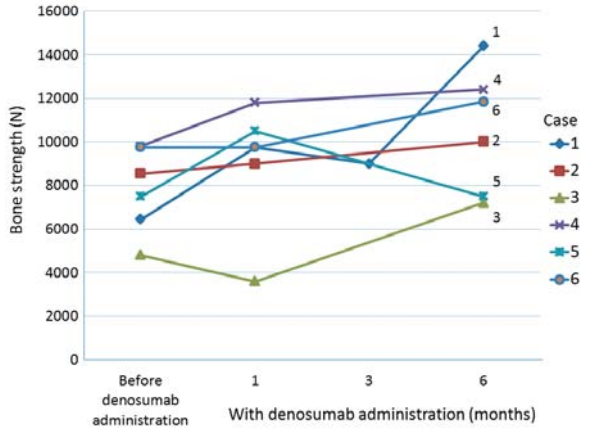

Figure 2. *Bone strength before denosumab administration and after 6 months. Repeated measures analysis of variance, p=0.005.*

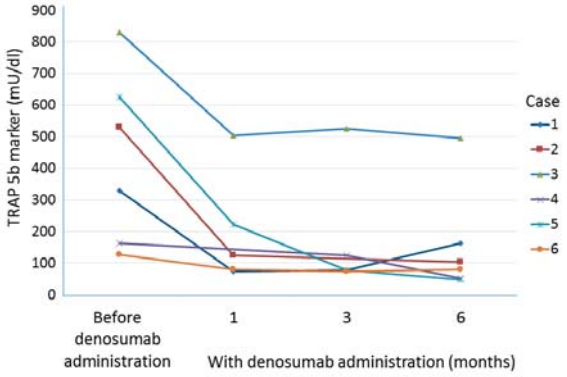

Figure 4. *The result of time-dependent change of tartrate-resistant acid phosphatase 5b (TRAP5b) marker. Repeated measures analysis of variance, p=0.0142.*

7500 N, and the average bone strength after 6 months; administration was 10600 N (Figure 2). The yellow arrow in Figure 3 shows the site of bone failure in case 1 before and after 6 months of denosumab administration. Statistical significance of differences in bone strength was evaluated with repeated measures ANOVA. Vertebral bony metastases showed a significant increase (p=0.0055, F=10.67). On the contrary, bone strength of the adjacent vertebral bone with no metastasis did not show a significant increase.

The analysis of bone resorption markers (TRAP-5b and urinary NTx) demonstrated a decrease in both markers as a result of denosumab administration (Figures 4 and 5). In our study, SRE such as fracture or paralysis did not occur up to 6 months after denosumab administration. In addition, the NRS score improved in all cases, namely that pain decreased.

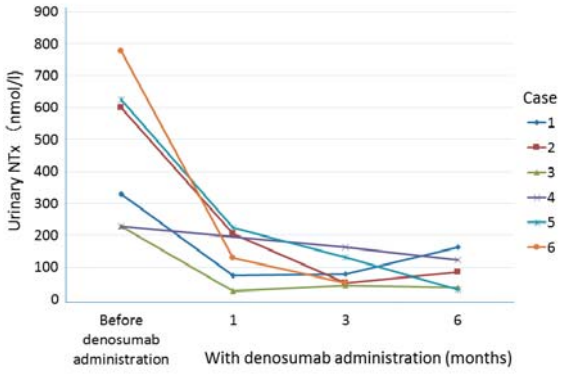

Figure 5. *The result of time-dependent change of urinary cross-linked N-telopeptide of type 1 collagen (NTx) marker. Repeated measures analysis of variance, p=0.0071.*

Discussion

Our study evaluated the reputed SRE-preventative effects of denosumab against the standard of bone strength by CT-based FEM, demonstrating an increase in bone strength over time in vertebral metastatic bone and maintenance of bone strength in non-metastatic bone. The study applied FEM to human metastatic bone, and to our knowledge, this is the first article to substantiate the effects of the SRE-preventative drug denosumab.

The suitability of using CT images and FEM as a basis for bone strength analysis has been previously verified in the osteoporosis field through the strong correlation between fracture strength of proximal femur in cadavers and fracture strength as analyzed using CT-based FEM simulations (14). The same method of analysis was used for metastatic bone tumors in this study, but the demonstration experiment's data previously applied to metastatic bone was lacking. Therefore, bone strength was established from using neighboring non-metastatic sections of the vertebral body as a control, and then this study tracked changes in bone strength over time in these sections as well as in metastatic sections. We examined features of imaging findings in diseased vertebral body sections from five cases of osteolytic lesions and one case of mixed osteolytic and osteosclerotic sections before denosumab administration. The five cases with osteolytic changes all exhibited osteosclerotic findings after six months, with bone strength significantly increased in four of them. There was no observable increase in bone strength in the remaining case (case 5), which had bone loss. The one case with mixed osteosclerotic and osteolytic lesions before denosumab administration exhibited osteosclerosis and increased bone strength after 6 months. In contrast to these image changes in metastatic sections of the vertebral body, the neighboring non-metastatic sections of the vertebral body displayed neither image changes nor any significant changes in bone strength over 6 months. These results, combined with the confirmed inhibition of bone resorption markers and improvement in pain, suggest that administration of denosumab inhibited the activity of osteoclasts that had been increasing in the metastatic sections of the vertebral body and brought about a favorable state of osteoblasts, achieving osteosclerosis and an increase in bone strength. However, as seen previously in the literature, bone loss in sections of the vertebral body affected by tumors is a significant factor in bone strength reduction, that also suggests that achieving an increase in bone strength in these cases is difficult (15).

With regard to the result of no changes in bone strength in neighboring non-metastatic lesions of the vertebral body, the results of previous studies on osteoporosis serve as a reference. When the results of this study are considered together with those of previous research, for example from a prospective study in which 33 patients administered alendronate exhibited significantly increased bone strength after 12 months (16), a randomized controlled trial on postmenopausal osteoporosis that demonstrated a 4.2% reduction in bone strength 36 months later for patients administered a placebo (n=48) as opposed to an 18.2% increase in bone strength for those administered denosumab (n=51) (17), and a study that did not observe any significant difference in bone strength until 12 months after treatment with either denosumab or a placebo (18), it is suggested that the principal factor in the absence of demonstrated changes in bone strength in non-metastatic lesions of vertebral body in this study was the short follow-up phase. In the future, long-term tracking of bone strength following intervention with denosumab will be necessary.

On the other hand, adverse events have been reported in a certain proportion of cases following administration with denosumab (19). One new finding obtained in this study, namely that inhibition of bone resorption and resulting osteosclerosis and further increase in bone strength caused by intervention with denosumab stabilizes and improves pain in the vertebral column, is undoubtedly a valid treatment intervention for maintaining quality of life and ADL in the terminal phase of stage IV solid cancer. Fortunately, no adverse events were observed in this case series, although a certain number of adverse events would be expected in studies with larger sample sizes. In conclusion, we consider that the benefits of denosumab administration for metastatic bone cancer exceed the risks.

Study limitation. As was shown in the discussion so far, the present study has a number of limitations: i) There was no validation for bone metastases. ii) There was a large variation in the cancer and clinical background of patients, so no verification could be made as to whether effects resulted from the intervention of denosumab or from other factors. iii) There was no consideration of the material properties of metastasizing bone. iv) The number of cases was small.

Future plan. Taking into account these study limitations, we have established the following plan for the future. i) Obtain validation for the FEM analysis of metastatic bone tumors. ii) Accumulate data for all adjuvants, stages, and cancer types. iii) Investigate in the long term whether primary bone strength could be a surrogate for predicting subsequent SREs, and determine appropriate criteria for use of denosumab.

Conclusion

The present study is, as far as we know, the first to apply CT-based FEM to bone metastases. There is some room for improvement regarding the reliability of its results, but with the effect of successive bone strength increase through denosumab intervention for stage IV cancer cases, bone

turnover marker inhibition and improved subjective symptoms, there is the possibility that CT-based FEM will be an extremely useful assessment method in improving quality of life in the final stages of cancer.

Conflicts of Interest/Disclosure

Sources of funding Authors report no conflict of interest concerning the materials or methods used in this study, nor in the findings specified in this article.

No benefits in any form have been or will be received from a commercial entity related directly or indirectly to the subject of this article.

References

1 Smith MR, Saad F, Coleman R, Shore N, Fizazi K, Tombal B, Miller K, Sieber P, Karsh L, Damiao R, Tammela TL, Egerdie B, Van Poppel H, Chin J, Morote J, Gomez-Veiga F, Borkowski T, Ye Z, Kupic A, Dansey R and Goessl C: Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase III, randomised, placebo-controlled trial. Lancet *379*: 39-46, 2012.

2 Keyak JH, Skinner HB and Fleming JA: Effect of force direction on femoral fracture load for two types of loading conditions. J Orthop Res *19*: 539-544, 2001.

3 Keyak JH, Rossi SA, Jones KA and Skinner HB: Prediction of femoral fracture load using automated finite element modeling. J Biomech *31*: 125-133, 1998.

4 Keyak JH, Rossi SA, Jones KA, Les CM and Skinner HB: Prediction of fracture location in the proximal femur using finite element models. Med Eng Phys *23*: 657-664, 2001.

5 Lotz JC, Cheal EJ, and Hayes WC: Fracture prediction for the proximal femur using finite element models: Part II–Nonlinear analysis. J Biomech Eng *113*: 361-365, 1991.

6 Ansher SS, Scharf R, and Cancer Therapy Evaluation Program at the National Cancr I: The Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute: industry collaborations in new agent development. Ann NY Acad Sci *949*: 333-340, 2001.

7 Katagiri H, Okada R, Takagi T, Takahashi M, Murata H, Harada H, Nishimura T, Asakura H and Ogawa H: New prognostic factors and scoring system for patients with skeletal metastasis. Cancer Med *3*: 1359-1367, 2014.

8 Dougherty G and Newman D: Measurement of thickness and density of thin structures by computed tomography: a simulation study. Med Phys *26*: 1341-1348, 1999.

9 Keller TS: Predicting the compressive mechanical behavior of bone. J Biomech *27*: 1159-1168, 1994.

10 Reilly DT and Burstein AH: The elastic and ultimate properties of compact bone tissue. J Biomech *8*: 393-405, 1975.

11 Bayraktar HH, Morgan EF, Niebur GL, Morris GE, Wong EK, and Keaveny TM: Comparison of the elastic and yield properties of human femoral trabecular and cortical bone tissue. J Biomech *37*: 27-35, 2004.

12 McCalden RW, McGeough JA, Barker MB, and Court-Brown CM: Age-related changes in the tensile properties of cortical bone. The relative importance of changes in porosity, mineralization, and microstructure. J Bone Joint Surg Am *75*: 1193-1205, 1993.

13 Rohl L, Larsen E, Linde F, Odgaard A, and Jorgensen J: Tensile and compressive properties of cancellous bone. J Biomech *24*: 1143-1149, 1991.

14 Bessho M, Ohnishi I, Okazaki H, Sato W, Kominami H, Matsunaga S, and Nakamura K: Prediction of the strength and fracture location of the femoral neck by CT-based finite-element method: a preliminary study on patients with hip fracture. J Orthop Sci *9*: 545-550, 2004.

15 Sahli F, Cuellar J, Perez A, Fields AJ, Campos M, and Ramos-Grez J: Structural parameters determining the strength of the porcine vertebral body affected by tumours. Comput Methods Biomech Biomed Engin *18*: 890-899, 2015.

16 Imai K, Ohnishi I, Bessho M, and Nakamura K: Nonlinear finite element model predicts vertebral bone strength and fracture site. Spine *31*: 1789-1794, 2006.

17 Keaveny TM, McClung MR, Genant HK, Zanchetta JR, Kendler D, Brown JP, Goemaere S, Recknor C, Brandi ML, Eastell R, Kopperdahl DL, Engelke K, Fuerst T, Radcliffe HS, and Libanati C: Femoral and vertebral strength improvements in postmenopausal women with osteoporosis treated with denosumab. J Bone Miner Res *29*: 158-165, 2014.

18 Zysset P, Pahr D, Engelke K, Genant HK, McClung MR, Kendler DL, Recknor C, Kinzl M, Schwiedrzik J, Museyko O, Wang A, and Libanati C: Comparison of proximal femur and vertebral body strength improvements in the FREEDOM trial using an alternative finite element methodology. Bone *81*: 122-130, 2015.

19 Zhang X, Hamadeh IS, Song S, Katz J, Moreb JS, Langaee TY, Lesko LJ, and Gong Y: Osteonecrosis of the Jaw in the United States Food and Drug Administration's Adverse Event Reporting System (FAERS). J Bone Miner Res 2015 doi: 10.1002/jbmr.2693. [Epub ahead of print]

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