A Case of Breast Cancer Associated with Multiple Bone Metastases Successfully Treated with Denosumab and Capecitabine

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The case is a 76-year-old woman, who consulted our hospital due to back pain and bilateral costalgia. She was diagnosed with multiple bone metastases of the right breast cancer upon close examinations. The result of a needle biopsy indicated a human epidermal growth factor receptor-2 (HER2) enriched type papillotubular carcinoma. Treatment due to trastuzumab was not suitable because of poor cardiac function, leading to the selection of a denosumab-administration regimen against systemic bone metastases in addition to capecitabine. Denosumab was subcutaneously injected in 120 mg doses every 4 weeks, and oral administration of capecitabine at 1,200 mg/day (administration for 3 weeks and 1 week drug withdrawal) was initiated from the second denosumab administration onwards. After initiation of the combination therapy of denosumab and capecitabine, the levels of tumor markers were gradually decreased, accordingly, the tumor size in the right breast was regressed. The patient's general condition was also significantly improved. Few adverse events were recognized in combined therapy using denosumab and capecitabine, and it was believed to have high efficacy and tolerability in cases with poor performance status.

Key words: denosumab, capecitabine, breast cancer, bone metastasis

Introduction

Varieties of multidisciplinary therapies are carried out with the objective of reducing skeletal-related events (SRE) as well as pain relief against bone metastasis from breast cancer. Multidisciplinary therapy, including anticancer drugs, hormones, molecular targeting agents, radiation therapy, bone resorption inhibitors and orthopedic surgery, is often applied; however, not all therapies are necessarily capable of being carried out depending on the general condition of the patient.

We hereby report on our experience regarding a case in which denosumab and capecitabine were administered at reduced dosages in a case of bone metastasis from breast cancer having poor cardiac function, thereby succeeding in prominently improving the general condition and bone metastasis symptoms.

Case

The patient was a 76-year-old female who visited a local orthopedic clinic for the treatment of back pain and bilateral costalgia at the end of 2011. She was referred to the Orthopedics Department of our hospital in May 2012 due to the persistence of pain despite treatment. The presence of bone and axillary lymph node metastasis of breast cancer was suspected based on the findings of magnetic resonance imaging (MRI) and chest computed tomography (CT) scans obtained on admission, prompting the patient to consult our department. She was unable to walk due to lower back pain and instead used a wheelchair. Her performance status (PS) was 2 to 3 (an Eastern Cooperative Oncology Group (ECOG) PS of 2 indicates less than 50% of daytime hours spent in bed, while a PS of 3 indicates more than 50% of daytime hours spent in bed). The patient's past medical history was significant for hypertension, cardiac hypertrophy and atrial fibrillation. Her family history was not significant for malignancy in any first-degree relative. Meanwhile, the serum level of Nation Cancer Center–Stomach–439 (NCCST439) was within the normal range at 4.3 U/ml, while the carcinoembryonic
antigen (CEA) level was elevated at 165 ng/ml in association with a carbohydrate antigen 15-3 (CA15-3) level of > 300 U/ml. Mammography revealed areas of pleomorphic and fine, linear calcification with a segmental distribution in the upper outer quadrant of the right breast, assessed as Breast Imaging Reporting and Data System (BIRADS) category 5. In addition, mammary ultrasonography demonstrated a lobulated low echoic mass with an heterogeneous inner echo in the upper outer quadrant of the right breast. Moreover, multiple swollen lymph nodes were observed in the right axilla.

Bone scintigraphy disclosed multiple areas of accumulation in the skull, vertebral body, both sides of the costal bones, both shoulder bones, both humeral bones and pelvic bone. Additionally, a chest CT scan revealed a tumor with contrast enhancement in the right mammary gland as well as right axilla. Moreover, sclerotic changes and partial osteolytic changes were noted in the vertebral bodies and pelvic bones. A head CT scan showed tumor features suggestive of bone metastasis in the skull, although there were no findings of metastasis in the brain. A core needle biopsy was performed in June 2013, and histopathologic examination of the biopsy specimen revealed invasive papillotubular carcinoma, nuclear grade 2, histological grade 2, estrogen receptor negative, progesterone receptor negative, human epidermal growth factor receptor-2 (HER2) 3+, Ki67 30%, a so-called HER2 enriched type breast cancer. It was diagnosed as an indication for systemic therapy using trastuzumab at first; however, the ejection fraction (EF) decreased to 22% upon echocardiography, and moreover, the PS was poor, leading us to believe that treatment involving trastuzumab would be difficult. During an investigation into other therapies, a pathological fracture of the right collarbone was generated when the patient rolled over in bed at home. Therefore, she was admitted to the hospital for radiotherapy as medical treatment for the fracture. Following admission, oral administration of 10mg oxycontin was commenced for controlling pain and radiation exposure of 3Gy per time was carried out 10 times, totaling 30Gy irradiated against right collarbone fracture. Simultaneous with the initiation of radiotherapy, subcutaneous injection of 120 mg denosumab was commenced against systemic multiple bone metastases. Although combined therapy with capecitabine, which has a radiation sensitizing effect, was considered, intoxication dermatosis focusing on the back was generated before the administration of capecitabine. All oral administration other than antihypertensive drugs and oxycontin were discontinued, and oral treatment was commenced using steroids. As a result of the therapy, the intoxication
dermatosis remitted; however, the causative drug was not specified and her hospital stay was prolonged by approximately one week following termination of radiation therapy. The second course of subcutaneous injection of 120 mg denosumab was carried out in July 2013 following discharge. Subsequently, it was confirmed that there was no recurrence of intoxication dermatosis, and oral intake of capecitabine was commenced at half the normal quantity of 1,200 mg/day (administration for 3 weeks and 1 week drug withdrawal).

After commencement of the combined therapy using denosumab and capecitabine, pain in the right collarbone improved without any particular

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**Figure 2** Treatment course and changes of tumor markers

**Figure 3** Chest computed tomography

A reduced tumor in the right breast (indicated by a arrow) and reduced axillary lymph nodes (indicated by an arrowhead) were observed carried out 4 months following treatment.
adverse effects, and oral administration of oxycon- 
tin was discontinued one month. Subsequently, the 
tumor marker gradually declined (Figure-2), appe- 
tite improved along with this, and the patient 
recovered and was able to commute to the hospital 
by walking alone 3 months following the commence- 
ment of the treatment. A reduced tumor in the right 
breast and reduced axillary lymph node were 
observed upon chest CT carried out 4 months 
following treatment (Figure-3).

The tumor marker continued to decline thereaf- 
ther, the PS improved, and currently, in November 
2013, the patient is still undergoing combined 
therapy using denosumab and capecitabine on an 
outpatient basis.

**Discussion**

Breast cancer is known to generate bone 
metastasis at a high frequency among all solid 
carcinomas. Although it is rare for bone metastasis 
to become directly life threatening, it significantly 
lowers the quality of life (QOL) of patients due to 
pain and bone fractures. Accordingly, in addition to 
 systemic therapies such as chemotherapy and 
hormone therapy, multidisciplinary therapy, includ- 
ing bone resorption inhibitors, radiation therapy 
and orthopedic surgery, is often applied as treat- 
ment for bone metastasis of breast cancer.

Bone metastasis is generally established with a 
focus on the interrelationship of cancer cells and 
osteoclasts, and receptor activator of nuclear factor 
κB ligand (RANKL), which is a cytokine expressed 
in osteoblasts/bone marrow stromal cells, playing a 
major role in the differentiation, activation, and 
 survival of osteoclasts. Osteoclasts caused by bone 
metastasis is generated due to the cancer cells, 
bones, and stem cells in the bone marrow complexly 
interacting with each other. Cancer cells generate 
hormone-related substances and a variety of 
cytokines, promoting the expression of RANKL on 
the osteoblasts. When RANKL bonds with RANK 
on the osteoclasts, bone resorption is triggered and 
 various growth factors stored in the bone are 
released at this time. Cancer cells fall into a vicious 
cycle of using these growth factors to further 
proliferate. Moreover, recently, it has been 
suggested that RANKL-RANK is deeply involved 
in the reconstruction of mammary tissue and 
generation of breast cancer, and that RANKL 
causes the migration of breast cancer cells.

Denosumab is a human monoclonal antibody 
against RANKL which inhibits RANKL from 
binding with its receptor, RANK, thereby suppress- 
ing the effect of osteoclasts.

In a joint international randomized double blind 
comparative study involving 2,046 cases of bone 
metastasis patients suffering from breast cancer as 
the subjects, the period until the onset of initial SRE 
was predominantly prolonged in the denosumab 
group compared to the zoledronic acid (a bisphos- 
phonate) group [hazard ratio 0.82, p = 0.0074], 
with the period until SRE following the initial onset 
wards also predominantly prolonged in this 
group. Regarding pain, a 22% decline in the risk was 
observed within the period of transition from mild 
pain to moderate or serious pain felt by patients in 
the denosumab group [hazard ratio 0.78, p = 
0.0024]. Based on these results from clinical 
studies, denosumab was added to the 2011 guide- 
lines for the American Society of Clinical Oncology 
(ASCO) as a therapeutic drug against breast 
cancer accompanying bone metastasis, and 
moreover, denosumab is mentioned in the algo- 
 rithm for breast cancer along with zoledronic acid 
and pamidronic acid (a nitrogen-containing bis- 
phosphonate) in the 2011 edition of the Japanese 
guidelines for breast cancer treatment.

The present case was a hormone receptor-negat- 
ive breast cancer found with bone metastasis as the 
trigger. The PS was poor and such strong anti- 
cancer drugs as anthracycline and taxane, could not 
be selected. Moreover, the cardiac function was also 
poor, making it impossible to adopt trastuzumab. A 
 pathological fracture of the right collarbone was 
generated during close examination of the entire 
body, and so radiation exposure along with denosu- 
mab administration were preliminary carried out as 
a treatment involving pain control, and subsequent- 
ly, combined with the use of capecitabine, which 
may be relatively safely used as a 3rd 
 chemotherapy against recurrent and metastatic breast cancer, as 
systemic chemotherapy. Capecitabine was adminis- 
tered by approximately half the quantity due to 
problems with allergies, and the tumor marker 
dropped following the commencement of oral 
administration, leading to a better-than-expected 
effect being obtained.

In recent clinical studies, there have been many
Reports with regards to the prolongation of overall survival time (OS) and disease-free survival (DFS) due to concomitantly using zoledronic acid with standard therapies. It is believed that not only the SRE suppressing effect of zoledronic acid but also antitumor effects are involved in such prolongation of OS and DFS. Meanwhile, there are currently very few clinical experiences with denosumab and its antitumor effect is scarcely reported. However, it is unlikely that sufficient effect was obtained by capecitabine alone in the present case, thus leading us to hypothesize that denosumab may enhance the effects of capecitabine.

Although the PS and cardiac function were lowered in the present case, adverse events due to this regimen were hardly recognized, exhibiting high efficacy as well as tolerability. However, there are still few reports regarding combined therapy using denosumab and capecitabine, and it is believed that more cases need to be accumulated in the future.

References